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THE MONTH

The Symposium

THE care of the child is the most satisfying part of general practice. It is here that the family doctor comes into his own. In a very real sense he shares in the joys and the sorrows of the parents, and in many cases comes to be looked upon as the confidant of both them and their children—to whom they can all turn when they are in trouble. On the other hand this very privilege carries with it a heavy responsibility. Fortunately, the child is a resilient animal but when things go wrong the consequences can be so devastating in that they may lead to permanent crippling or chronic illness for life. It is to help the family doctor in caring for these young patients that we publish at least once a year a symposium dealing with some aspect of pædiatrics. This month it is 'Diseases of Childhood', and the conditions chosen for discussion are those in which early detection and adequate treatment in the early stages are of particular importance. It is not every contributor who can conclude on the same optimistic note as Professor Watkins in his article on 'Tuberculosis in Childhood', but all are able to bring helpful advice in the management of some of the more difficult problems of the sick and ailing child.

The Treatment of Leprosy

PERHAPS the most striking feature of the Seventh International Congress of Leprology, which was held in Tokyo last November, was the evidence it provided of the tremendous advance that has been made in the control of the disease during the last decade. As one speaker summed up the position: 'We are in fact living through a revolution in the history of leprosy . . . The leprosy worker has a cheap, simple and relatively effective basic treatment, capable of the widest application. Alternatives are available when needed and more may safely be predicted . . . For the patient, an entirely new situation has arisen . . . He now knows he is a man like anyone else. He may be able to lead a normal life while taking treatment and continue in his employment'.

Even the most cursory perusal of the report of the Congress published in the January issue of *Leprosy Review* provides ample justification of these claims. The sulphones are still the basis of therapy, but at least two promising new compounds were discussed at the session devoted to therapy—a diphenyl

thiourea compound (Ciba 1906) and a derivative of ethyl mercaptan, diethyl dithiol*iso*phthalate ('etusil'). To talk about a 'cure' for leprosy is still not justifiable, but the mere fact that drugs are now available which will keep the disease under control lends good ground for hope that one day an anti-leprosy drug will be found which will be as effective as the anti-tuberculous drugs have been in mastering the other mycobacterium which at one time played such havoc with mankind. Meanwhile it behoves all those concerned with leprosy to ensure that their efforts are carefully coordinated so that the problem is tackled on a sound scientific basis. Leprosy, it must never be forgotten, is not merely a medical problem; it is a vast social problem in which the only hope of success lies in the proper alignment of research worker, physician, surgeon, and social worker.

Medical Education in Russia

In an interesting review of medical education in Soviet Russia (*J. med. Educ.*, 1958, **33**, 827), Dr. Arnold Starr, of Harvard University, reports that there are 77 medical schools in the Soviet Union, all of which are under the jurisdiction of the Ministry of Health and have no official association with the universities. At present there are 152,000 students, 70 per cent. of whom are women, and they are taught by a staff of 16,411 professors and instructors. About 16,000 physicians graduate each year, and there is said to be a total of 329,442 physicians in the Union. This is compared with the position in 1917, when there were 16 medical institutes and a total of 19,800 physicians.

The medical curriculum consists of six academic years. The first two years are devoted to the basic sciences, philosophy and politics, and two languages (Latin and one modern foreign language). Clinical instruction begins in the third year and is continued throughout the remainder of the six years. At the end of the fourth year the students live for two months in a rural hospital. The basic instructional unit is a group of nine or ten students; this is organized in the first year and maintained throughout the entire course. On qualifying the young doctor is offered a position, usually in a rural community, by the Ministry of Health, but some 10 per cent. are offered the opportunity of continuing their medical education, and another 700 are selected for a three-year course in a medical or research institute, to develop their proficiency in experimental research. A course of post-graduate training is required for rural physicians every three years, and for urban physicians every four years. There are 11 postgraduate medical institutes which are attended by 16,000 physicians every year for periods of four to six months. In addition, 8000 physicians take a similar course of instruction in local community centres. Although Dr. Starr was impressed by 'the alertness and intelligence' of the medical students whom he met, he considers that in many respects 'the Soviet's attempts to integrate medical education with the needs of the Russian nation, be they medical, military,

political or economic, have compromised the high standards of intellectual freedom which have characterized the training of physicians in the Western world'.

Doctors and Drugs

LAST year there came into existence an organization which is a welcome sign of the increasing cooperation which is developing between the pharmaceutical industry and the medical profession in their joint task of ensuring that the best possible drugs are made available for the alleviation of disease. This is the Association of Medical Advisers in the Pharmaceutical Industry. The mere fact that the Association has over sixty members is an indication of the extent to which the industry has realized that it must have at its disposal a body of expert medical advice to ensure that its research work is being guided along the right lines and that all its new products receive adequate clinical trial before being made available for general use. The Association is entirely independent of the industry and has come into being as the result of the spontaneous desire of the medical advisers to be able to meet together and discuss problems of mutual interest.

The Association's first major venture—the symposium on 'Progress in the evaluation of new drugs', which was held in January—was an excellent example of the value of such an organization. It brought together the medical advisers of the pharmaceutical industry, leading clinicians, pharmacologists and statisticians, and allowed them to discuss the mutual problems involved in the clinical testing of new drugs. As Sir George Pickering, the Regius Professor of Medicine in the University of Oxford, pointed out in his final summing up of the discussion, the proceedings showed a high standard of integrity in the industry. With this auspicious start the new Association can look forward to playing an important part in the development of modern medicine.

Liquorice

Is liquorice going to prove to be yet another example of the old adage about there being nothing new under the sun? As the *Pharmaceutical Journal* (1959, **182**, 79) points out in an interesting review, it has been used by man for three millenniums, but for many years now it has been regarded by the clinical scientists as one of those 'household remedies' which, for some inexplicable reason, refused to disappear from *The British Pharmacopœia*. During the last decade, however, it has come to the fore as the centre of violent controversy, following reports that it has a cortisone-like action.

As is so often the case in such clinical controversies, both parties have right on their side, and both have erred in jumping to conclusions on inadequate data. An impartial review of the available evidence would seem to indicate that liquorice has an anti-inflammatory action. Whether or not this is obtained in man or the experimental animal depends upon the method

of preparation of the extract used. Briefly, the position is that the active principle of liquorice is the glycoside, glycyrrhizin. The derivative which has the cortisone-like, or anti-inflammatory, action is the aglycone of this glycoside—triterpene glycyrrhetinic acid, which has a chemical structure bearing some similarity to cortisone. Unfortunately, this acid exists in a number of isomeric forms, and much of the difficulty in achieving agreement as to its effect has been due to the use of preparations containing various mixtures of these isomers. Recent pharmacological reports indicate that, with a carefully standardized preparation, a consistent anti-inflammatory action can be obtained in the experimental animal. This being the case, the time has come for some research organization, within or without the pharmaceutical industry, to tackle the problem on a really comprehensive scale. If a standardized preparation, with a consistently anti-inflammatory action, can be produced at a reasonable cost, then its efficacy in rheumatic conditions and in dermatology should be investigated by means of controlled clinical trials.

The Taste of Water

Has water a specific taste? Such is the intriguing query raised by Y. Zotterman and H. Diamant (*Nature* (*Lond.*), 1959, **183**, 191). The conventional view hitherto has been that, to quote Professor Harry D. Patton ('A Textbook of Physiology', edited by John F. Fulton (1955), 17th edition, p. 377), 'four distinct gustatory submodulities are recognized: sweet, salt, bitter and sour or acid'. In 1949, however, Zotterman reported that water applied to the tongue of the frog elicited an electrical response from the glossopharyngeal nerve, and the conclusion was reached that this response was produced by specific fibres. A natural reaction to these findings seemed to be that these 'water' fibres subserved a special function in water regulation in amphibians living in fresh water. Subsequent investigations, however, revealed that cats, dogs, pigs and monkeys—but not rats—also possessed specific nerve fibres in the chorda tympani which respond to the application of water to the tongue.

Zotterman and Diamant have now had the opportunity to investigate the problem in man by recording the electrical response from the chorda tympani during operations for mobilization of the stapes. A good response was obtained to salt, sugar, quinine, and acetic acid but, in the case of water, there was a 'negative response'. In other words, as in the case of the rat, water abolished the spontaneous activity of the taste fibres. These preliminary findings therefore suggest that water has not a specific taste, so far as man is concerned. Its action, Zotterman and Diamant suggest, 'must be of negative character in that water abolishes or decreases the resting activity of taste fibres, particularly that of salt fibres'. 'The specific effect of water on taste in man', they conclude, 'can thus be looked upon as being of the same nature as that of blackness upon vision'.

CHRONIC PULMONARY INFECTIONS IN CHILDHOOD

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It is true, happily, that chronic pulmonary infections in childhood are rare. When they occur, however, they are important because any chronic illness in a child imposes on the parents and on the family doctor a duty of management as distinct from, and in addition to, the treatment of acute disease. Stresses arise when one member of a family is smitten with chronic illness: the whole household may come to be centred on the chronic invalid to the ultimate detriment of home life and the disadvantage of the patient. Such considerations as nursing, education and nutrition, climate and environment, as well as the more technical aspects of medical or surgical treatment are very much the concern of the family doctor. It is of great importance therefore that the diagnosis should be precise and accurate, and that the prognosis should be faced.

Pulmonary tuberculosis will not be dealt with in this article as it is considered elsewhere in this symposium, but this would appear to be the place to stress the importance of telling parents of children with non-tuberculous pulmonary infections that tuberculosis has been excluded. To the layman Koch's bacillus is still a dreaded enemy and reassurance on this point will often allay unspoken fears. At the same time it is right and needful to tell the parents of a child with a chronic pulmonary infection what measure of success can be expected, albeit often only by strict and painstaking management, possibly attended by a number of apparent setbacks. For its ultimate satisfactory conclusion the non-tuberculous chronic pulmonary infection is always a matter which calls for the long-term cooperation of parents and family doctor.

CHRONIC OR RECURRENT?

From the strictly medical point of view this can be quite an important distinction. The obvious and easily observable example is provided by the tonsil which may usefully survive a number of acute infections—provided it does survive them and returns to healthy normality between attacks. This is the tonsil that should *not* be removed. But the chronically infected tonsil can be the source of repeated infections of the lower respiratory tract and should be removed. Chronic pulmonary infections can be, and very often are, the ultimate result of chronic upper respiratory tract infection. Indeed this is probably the most common cause of chronic pulmonary infection. The first steps in the prevention of chronic pulmonary infection in childhood must therefore be directed to the prevention or eradication of chronic upper respiratory tract infection.

CHRONIC UPPER RESPIRATORY INFECTIONS

Chronic *tonsillar* infection will be recognized by inspection of the tonsils. They will have been the site of repeated acute infections and, inspected not less than six weeks after the last acute infection, will be seen as either small, scarred and fibrous or hypertrophied and 'craggy', with inspissated pus in their crypts. Usually the tonsillar glands in the anterior triangles of the neck will be enlarged. Often the mother will complain of her child's foul breath.

Chronic *adenoid* infection may cause a purulent post-nasal drip which can be directly observed as a stream of muco-pus hanging down the posterior pharyngeal wall. Often the resultant hypertrophy of the adenoid tissue will reveal itself by nasal airway obstruction, sometimes with the characteristic 'adenoid voice', and loss of appetite, due to loss of a sense of smell. Food is dull without olfactory perception.

The adenoid hypertrophy may also cause obstruction of the ostia of the *para-nasal sinuses* and repeated episodes of acute sinusitis may lead to a chronic sinus infection. Fuller mention of this will be made later. Another manifestation of adenoid hypertrophy which may be of diagnostic value is recurring catarrhal middle-ear infection due to blocking of the outlets of the Eustachian tubes.

The traditional stupidity and backwardness at school of the sufferer from adenoid hypertrophy may be as much due to some degree of deafness as to the open-mouthed 'gormless' look of nasal obstruction. These very common symptoms should not only confirm the diagnosis of a chronic upper respiratory infection, but warn us that we are faced with a situation which, if not wisely handled, can lead to chronic pulmonary infection.

Chronic or repeated subacute sinus infection in childhood is much more common and more important than has been generally recognized (in spite of the authoritative observations on the subject by Crooks (1936) and others). Crooks pointed out that there was good reason to consider some cases of chronic adenoid infection as *secondary* to sinus infection although the opposite sequence is commonly assumed. When the condition of chronic sinusitis exists it is responsible for a quite striking condition of chronic ill health and lassitude in the patient, with an equally striking lack of localizing signs and symptoms. The sinuses commonly involved in childhood are the maxillary antra and, to a less extent, the ethmoidal air cells. The frontal and sphenoidal sinuses are of much less importance in this connexion, possibly because their full development occurs later in childhood.

Diagnosis and treatment.—If transillumination or skilled radiography fail to make the diagnosis, proof-puncture, with bacteriological investigation of the fluid thereby obtained, is of great value. Polythene intubation of provedly infected antra can give dramatically satisfactory results.

An eight-year-old patient of mine, referred for listlessness, lack of appetite, recurring colds and general debility, interrupted his busy eating, twenty-four hours after drainage, and with the polythene tubes still *in situ*, to tell me 'I haven't felt so well for years!'

Fortunately surgeons seldom now advocate the old, classical operations

for permanent drainage of the antra in children. The results of such operations have been, generally speaking, something worse than disappointing. Conservative treatment, with drainage through the natural ostia, chemotherapy or appropriate antibiotics, combined with short-wave diathermy can achieve better results.

The diagnosis of these chronic upper respiratory infections of childhood can be facilitated by skilled radiography. 'Soft' rœntgenograms of the sinuses and of a lateral view of the post-nasal space can be of great diagnostic value; but these pictures are best made by radiographers and interpreted by radiologists with experience in this skilled and specialized pædiatric field.

STAPHYLOCOCCAL PNEUMONIA

In early infancy local infection with virulent staphylococci is not uncommon. Happily this usually remains a local infection: in the umbilicus, the skin, or as conjunctivitis, rhinitis or paronychia. Wherever and whenever it occurs it deserves energetic treatment because of the danger of a staphylococcal respiratory infection. This usually manifests itself as an acute infection of the lungs, which may be complicated by abscess formation, by empyema or by pyo-pneumothorax. The resulting fibrosis and chest deformity are factors predisposing to chronic pulmonary infection.

The reason for the peculiar danger and severity of this infection is that the staphylococcus responsible is often an organism which has been acquired in hospital and has achieved resistance to the commoner antibiotics, particularly to penicillin. The most refined techniques of modern bacteriology are needed to identify the sensitivity of the organism and to guide treatment. Before the days of chemotherapy and antibiotics, staphylococcal pneumonia was almost always a fatal disease in infancy. In the early days of penicillin the mortality fell dramatically. Now, with the penicillin-resistant strains appearing, recent series of cases have been reported with mortality rates of up to 50 per cent.

BRONCHIECTASIS

This is the condition which, above all others, fulfils the definition of a true chronic pulmonary infection occurring in childhood. It is agreed that the two common etiological factors of this condition are, first, repeated or chronic infections, usually stemming from the upper respiratory tract and, secondly, bronchial occlusion with secondary segmental pulmonary atelectasis. The bronchial occlusion may be caused by the inhalation of infected material from the upper respiratory tract, or it may be associated with partial occlusion of a bronchus or bronchiole by pressure from enlarged, possibly tuberculous, peri-bronchial glands. An inhaled foreign body or tuberculous granulation tissue, acting as a foreign body, may be the obstructing agent. A further possible cause of bronchial blockage is swelling of the bronchial mucosa by infection or allergy. Interstitial pulmonary fibrosis may cause crowding and kinking of bronchi which will favour occlusion. The essential

factor in the production of bronchiectasis, however, is damage to the bronchial wall by infection.

The onset of the established condition is gradual, arrestable and, probably sometimes reversible in its earlier stages, when collapse of the lung still exists. We are indebted to Franklin (1958) for a long-term follow-up of bronchiectasis in childhood which gives grounds for a much more cheerful prognosis than was conventional before this work was published.

Diagnosis.—The diagnosis of bronchiectasis depends upon bronchography; otherwise the definitive diagnosis can hardly be made at a satisfactorily early stage even by careful history-taking or by repeated clinical examination; but both are essential if a proper selection of cases for bronchography is to be made. The history will be that the child has a chronic, productive cough. This symptom may have followed a definite acute infection such as measles, whooping-cough, and broncho-pneumonia. But there may be no such definite episode of illness to mark the onset. A persistent or recurrent upper respiratory infection or attacks of bronchial asthma may be the indications for further investigation. In 32.8 per cent. of Franklin's 171 cases no acute illness marked the onset of the condition, and in 99 cases the onset occurred under the age of two years.

The general condition of a child in the early stages of bronchiectasis is often quite good. Cyanosis is only present in severe and extensive cases, but finger-clubbing may be seen in some degree in about half the patients. The findings on clinical examination of the chest vary widely from time to time. Faulty posture and chest deformity are commonly seen. But changes in percussion note, air entry and the character of the breath sounds are notably inconstant. An area of dullness will be present where a region of atelectatic lung persists, and fine crepitations will be present later in the same area during re-aeration. Strictly speaking, coarse adventitious sounds and rhonchi which shift or alter their pitch on coughing or change of posture are signs of bronchitis, although they will nearly always be present from time to time in the untreated case of bronchiectasis. Rhonchi which do not shift during the examination are more likely to be associated with bronchial narrowing, due to localized mucosal swelling, bronchospasm or bronchial scarring. The very inconstancy of the physical signs in bronchiectasis is of diagnostic value.

TREATMENT

The diagnosis once made, the handling of the individual patient will depend upon many factors: the stage and extent of the disease, the general health of the child, the standard of housing, the ability of the parents to cooperate and the facilities for continued schooling, to mention but a few. The factors are obviously interrelated and nobody is more likely to be able to view the individual's situation as a whole, and to assess it, than the family doctor.

To take but one of these factors: the ability of the parents to cooperate. Here the question of the family budget will arise: do both parents have to

go to work? Is the child able to have a room of his own? Are the parents taking too gloomy or too complacent a view of the outcome? The first major decision is whether or not the patient can continue at home. In many cases it will probably be necessary to take the child into hospital at first for an energetic effort to clear up chronic upper respiratory infection and to institute postural drainage and physiotherapy. Bronchoscopic drainage may be needed to remove accumulated secretions and to permit atelectatic areas of lung to expand.

It is at about this stage in the management that a decision will have to be made as to whether surgical removal of the affected areas of lung has anything to offer. It has been said that in those cases with continuing symptoms and the bronchial lesions localized to a single lobe or segment, surgery offers such good hopes of permanent cure that it should be undertaken. Clearly, lesions may be so extensive and scattered through both lungs that surgery is not possible. The difficult decisions arise when the lesion is localized but the child's health is good. Surgery in such a case is, in a sense, prophylactic, but the results of medical treatment are usually good, provided the other criteria of good home management are fulfilled.

If they are not, treatment in a suitable residential school will have to be considered as an alternative to surgery. The disadvantage to the child of separation from home over long periods is much canvassed at present. But it has to be weighed against the possible failure of therapy conducted ineffectively in unsuitable home surroundings. In his review of cases treated at the Meath School of Recovery (the children were between 5 and 8 years of age) Franklin writes:—

> 'The prognosis of any chronic or disabling disease cannot be made on a purely anatomical basis . . . The doctor's advice, as well as his methods of diagnosis and treatment, may affect the situation in unintended ways. The only unmanageable boy had been away from home continuously from the age of 10 months to 5 years because of respiratory illness. Twenty-nine other patients were separated from home in early life for long periods on medical advice, though only four of these were led by behaviour disturbance to the Child Guidance Clinic. In six cases great fear of the disease had been induced in parents and children by the doctor's terrible prognosis or by his arguments in favour of surgery. Repeated bronchograms, radiographs and surgical operations take a toll of morale'.

These words are quoted to emphasize the importance of wisdom in the management of chronic illness. Thoroughness must not be confused with fussiness or with mere clinical curiosity. A test or a diagnostic manœuvre, whether it be a simple blood count, erythrocyte sedimentation rate or tuberculin test or a more elaborate procedure such as a bronchogram, should not be undertaken before answering the question: 'How will the result, whatever it may be, affect the management of the case?' And the answer to that question must be set against the question: 'How will the carrying out of this diagnostic procedure affect my patient?'

The subject of chronic pulmonary infection in childhood cannot be left without mentioning a few rare conditions which may crop up in practice, and can be recognized by those who are aware of their existence.

MUCOVISCIDOSIS

This is an inborn abnormality of the mucous glands throughout the body. In the newborn it may declare itself by the intestinal obstructive picture of meconium ileus. Later, fibrocystic disease of the pancreas may present the clinical picture of an infant who fails to gain weight at the normal rate, though normally hungry and taking food well, and who passes bulky, pale, offensive, fat-laden stools. In such cases it is found, by testing the stool and the duodenal juice, that the pancreatic secretion is deficient in trypsin, and that protein and fat digestion is at fault. In a large proportion of such cases the fibrocystic change is present in the lungs from early infancy and chronic pulmonary infection asserts itself.

The giving of pancreatin by mouth often greatly improves the nutritional situation and to that extent enables the patient to cope better with the chronic pulmonary infection. But such treatment does not affect the underlying abnormality of the lungs, which was held to be responsible for 130 out of 145 deaths in a series of 325 cases (di Sant'Agnese, 1956).

The diagnosis of the pulmonary abnormality, though often suggested by the history, the family history and by x-rays, depends upon the recognition of the associated pancreatic defect. This is achieved by obtaining samples of duodenal juice by per-oral intubation, and estimating its tryptic activity. A preliminary screening test may be carried out by estimating the ability of the stools to digest gelatin: progressive dilutions of a fresh stool specimen are incubated in contact with exposed photographic film. Tryptic activity is shown by the fact that the pigmented gelatin layer of the film is digested.

A further observation which may be turned to diagnostic use in this condition is that the sweat of affected children, instead of containing the normal 4 to 60 mEq. of chloride and 10 to 80 mEq. of sodium, contains 50 to 160 mEq. of chloride and 80 to 190 mEq. of sodium; approximately 20 per cent. of the patient's relations also show this abnormality.

Sweat is collected by placing a 3-inch (7.5 cm.) square of gauze on the child's back. This is covered with a larger piece of plastic sheeting and the child placed in a plastic bag or suit, covered with a blanket and allowed to sweat for thirty to ninety minutes. He is then taken from the bag and the sweat-soaked pad is placed in a stoppered Erlenmeyer flask. The weight and electrolyte content of the sweat are then estimated.

A more simple screening test known as the 'finger test' is also used.

A drop of silver nitrate is placed on Watman no. 2 filter paper. This is then placed between the thumb and forefinger or between both great toes of the patient. Firm pressure is applied for about a minute, then, a drop of 20 per cent. potassium chromate is added. A clear area at the site of pressure is due to the excess chloride combining with the silver nitrate.

This test is only positive in affected infants over twelve months.

PULMONARY HÆMOSIDEROSIS

This is another rarity in which the child may suffer from periodic attacks of dyspnœa, cyanosis and even hæmoptysis. The cause in infancy is not known, but the condition results not only in deposits of hæmosiderin in the elastic tissues of lungs and bronchioles, but in an iron-deficiency anæmia

which, together with the underlying pulmonary damage, may result in repeated or chronic pulmonary infection.

The diagnosis is suggested by the soft mottling of the lung fields seen on the x-ray and is confirmed by the finding in the sputum or gastric washings of cells (macrophages) containing granules with the characteristic staining properties of hæmosiderin.

A similar condition occurring later in life as a result of pulmonary hypertension, especially in association with mitral stenosis, leads one to speculate on a possibly similar exudative phenomenon as the cause of hyaline membrane disease in the newborn.

TREATMENT OF ACUTE EXACERBATIONS

Whatever the underlying lesion, the chronic pulmonary infections of childhood are characterized by acute exacerbations which, even when they are not serious or fatal, tend to a deterioration of the predisposing condition. The use of prophylactic antibiotics, combined with physiotherapy, can reduce considerably the frequency, morbidity and mortality of such complications. Continuous therapy with chlortetracycline or oxytetracycline in a dosage of 5 to 15 mg./kg. body weight per day is the usual method; mild cases may only need prophylaxis during the winter months. Added vitamin supplements are even more important with this treatment. Alternating antibiotics in the hope of preventing resistant strains has not been found to be of any value. In severe relapses aerosols such as 'alevaire' combined with an antibiotic such as neomycin are effective when used with systemic antibiotics.

CONCLUSION

Chronic disease in childhood constitutes a problem for the family which can only be successfully resolved with the wise help of the family doctor. Anxiety has to be kept at the appropriate level; unjustified despondency on the one hand and undue complacency on the other are calculated to hinder the 'consummation devoutly to be wish'd'. A diagnosis must be made on which a reasonably accurate prognosis can be founded. The making of the diagnosis may involve consultations, periods in hospital and a number of special and sometimes irksome, investigations. All this has to be foretold and explained. The successful handling of the patient can only be wisely determined by one who has a close knowledge of the parents, their capabilities, their responsibilities, their physical circumstances and their temperaments.

Along with this 'background' knowledge of the family, the doctor must be familiar with the various agencies—medical and social, local and national, educational and therapeutic—which can help him to enable his patient to make the best of a situation which is usually grave but often has a rewarding outcome.

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TUBERCULOSIS IN CHILDHOOD

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The pattern of tuberculosis in childhood has changed so dramatically in the last ten years that the general practitioner's approach to the problem must now be primarily one of detection and prevention rather than treatment of the established disease. Detection must include not only the infected case but also the child at risk. Perhaps one of the most important lessons that has been brought home to us about tuberculosis is that it is, at any rate so far as children are concerned, *an infectious disease* caught by contact with an infected adult. It is surprising to look back and realize how slow we have been in recognizing this fundamental etiology and all that it implies. It is true that bovine tuberculosis from drinking infected milk was, until a few years ago, a common cause of tuberculous infection of bones, joints and glands. With the virtual clearing in this country of tuberculosis-infected milk this type of infection has practically disappeared. Nevertheless it is probable that a fairly high percentage of those children thought to be infected with the bovine strain were in fact infected by the human strain. This view is supported by the large amount of bone tuberculosis, especially of the spine, found today in countries where there is no problem of infected milk because there are no cows to provide it. This is especially true of the Far East in such places as Hong Kong and Borneo where human infection is such a major problem.

INCIDENCE

We are fortunate indeed that in this part of the world it would seem probable that childhood tuberculosis will be a rare disease in the not too distant future. Since the last war there has been a steady decline in its incidence which has been greatly accelerated by the introduction of chemotherapy, improved housing and better economic and social conditions, together with BCG vaccination and the control or segregation of infected adults. Doctors are becoming less familiar with tuberculous disease and the present-day student may well qualify without experience of tuberculous meningitis or miliary disease. The battle is not yet won, however, and prevention and detection must continue with increasing vigilance as the incidence decreases. In spite of chest clinics, hospitals, health services and the like, the general practitioner is still often the first person to whom a child is referred with symptoms, and recognition of these plus an alertness to the possibility of tuberculous infection must be maintained. It is important that the child who has been infected with the tubercle bacillus should be readily recognized

before he develops manifest signs of the disease, and to this end the following points are of importance and worthy of discussion.

CONTACTS

Let us first rid ourselves of the far too common habit of inquiry into the family history only. Whilst the family is obviously the closest contact and source of infection, others tend to be disregarded, such as the lodger, schoolteacher and friends. There are authentic cases described of children developing tuberculous disease after such a short contact as sharing an air-raid shelter for a night with an infected adult. There is also the tragic story of three children who, one after the other, died of tuberculous meningitis through sharing the lodger's bedroom. Epidemics have been described in schools from a teacher with a positive sputum. It is the Sunday School teacher and the teacher of the very young who are the most dangerous because of their closer proximity to the child in supervising his work. An interesting example of the relative infectivity of tuberculosis is illustrated by the finding that in a certain leprosy colony in the West Indies a tuberculous schoolteacher infected five of the children, but remained free of leprosy herself. At the beginning of the war in 1939 a great number of our sanatoria were emptied in order to be free to accept bombing casualties which happily never came, but this dissemination of phthisical adults resulted in an alarming increase in tuberculous meningitis throughout the country.

No stone should be left unturned to try to find a possible contact and many adult cases have been revealed in this way, they themselves being often unaware of their own disease. The problem may also be approached from the other direction: that is to say that on finding an infected adult, all childhood contacts should be examined, tuberculin tested and, if necessary, x-rayed. This kind of follow-up is primarily the responsibility of the chest clinics, but the general practitioner must be ready to pass on relevant information and to see that the contact children are available and willing to be examined. By careful, and often prolonged, search for all those children who have been known contacts of the infected adult, lives have been saved and the disease has been prevented. When found, the infected adult should be removed from contact with children either by admission to hospital or some sort of social isolation until such time as his sputum is rendered negative. The tracing and handling of contacts is often laborious and time consuming but its importance justifies the effort.

TUBERCULIN TESTING

Of the various techniques employed, in our view the Mantoux test is the most reliable. The Heaf test is much easier to perform but not quite so easy to interpret and does not readily allow the occasionally helpful quantitative test which can be done with the Mantoux test by using different strengths

of old tuberculin. To perform the Mantoux test accurately requires practice and skill in giving intradermal injections to small children, but competently done it causes minimal discomfort.

A positive tuberculin reaction implies a state of sensitivity to the tubercle bacillus, which means in effect that the child has been infected. How far this sensitivity runs parallel with the degree of immunity is still not accurately defined. The conversion to a positive tuberculin reaction may be entirely symptomless and in fact is so in the vast majority of children, but the finding of a positive test in any child under 5 years of age or in a child who is a known contact with an infected adult, or in a child of any age with suspicious symptoms or signs, is a physical sign of supreme significance. We must remember, however, that children who have been successfully vaccinated with BCG will also give a positive tuberculin test.

Positive tuberculin test in a child under 5 years old.—The younger the child who becomes infected with the tubercle bacillus, the more risk there is of a pulmonary, meningeal or blood-stream spread. It is therefore essential that such a child should be carefully examined and have his chest x-rayed. This state of affairs immediately raises a difficult clinical and therapeutic problem. Should one treat all such children with a full course of chemotherapy even though there is nothing more than a positive test with no clinical or radiological evidence of disease? There is some debate on this but it would appear that the majority opinion is that all children under three years old should be given a course of therapy and that those over three, without signs or symptoms, should be watched carefully but not necessarily given active treatment. Those with radiological or other signs must, of course, be treated. Methods of treatment will be discussed later.

Child of any age with active contact history.—It would be tempting Providence a little too far not to offer such a child a full course of treatment even if little evidence of disease is found.

Child with clinical evidence of tuberculous infection.—This really warrants a description of how this may present and this would seem to be the appropriate place for a simple review of the ways in which tuberculous disease may occur in childhood. We have already considered those who are found on routine or contact testing to be tuberculin positive and those children found to be infected on x-ray examination of the chest either as a routine measure or as an incidental finding. To these must be added those cases presenting with clinical signs and symptoms of the disease, together with radiological findings.

CLINICAL SIGNS AND SYMPTOMS OF TUBERCULOUS INFECTION

General.—This would include the classical story of tiredness, loss of weight and low-grade fever. Cough is seldom a prominent or presenting feature. In fact a child with a cough is far more likely to have a non-tuberculous

lung lesion such as asthma, collapsed lobe or bronchiectasis. Another symptom that causes lay anxiety is night sweats. These are seldom, if ever, associated with this disease and are in fact perfectly normal phenomena in a great number of children. Night sweats are in any case badly named, for the sweating occurs during sleep and not necessarily at night, so that the late Marcus Paterson renamed the condition 'slumber sweats'. General symptoms may be vague and minimal so that they tend to pass unrecognized.

Local.—(a) *Chest.*—Unless there is some spread from the original primary complex, signs in the chest are most difficult to detect. The exception to this is the child with a pleural effusion, a rare manifestation under the age of five years. The hilar glands of the primary complex, however, may enlarge and cause signs and symptoms either by pressing on, or by rupturing into, a bronchus, giving rise to tuberculous pneumonia. In the former case this may produce wheezing respiratory distress with clinical and radiological signs of obstructive emphysema, and in the latter physical signs may be minimal but x-rays may show a shadow previously labelled as 'epituberculosis'. This shadow has now been shown to be due to a tuberculous pneumonic process in a lobe or lung segment and not a simple collapse as was previously thought.

(b) *Glands.*—The commonest site, other than the hilum, is in the neck. Abdominal tuberculous glands have become a rarity.

(c) *Meninges.*—Tuberculous meningitis is becoming so much less common that its detection will catch out the unwary. The danger period is within the first six months of the primary infection, and prompt therapy as soon as tuberculin conversion is known to have taken place, together with BCG vaccination of all negative contacts, has done much to remove this menace altogether. To those of us who recall this dread disease before the use of streptomycin, this is one of the miracles of modern medicine. Early diagnosis is of the utmost importance for the prognosis depends so much upon starting treatment early, at least before the child becomes unconscious. A diagnostic lumbar puncture in cases of doubt is always justifiable.

(d) *Bones and joints.*—Early signs are never easy to detect but a positive tuberculin reaction in the absence of previous BCG vaccination may be more helpful than a biopsy. As human infection is more likely at the present time, it is important to x-ray the chest in all cases.

ALLERGIC MANIFESTATIONS

Erythema nodosum.—This is one of the commonest ways in which primary infection may show itself. In children there is little doubt that the cause of this syndrome must be considered tuberculous unless proved otherwise. There is no evidence that this condition is a symptom of rheumatic infection. I have never seen erythema nodosum in a child with rheumatic disease, nor have I seen a case of erythema nodosum develop any other signs associated with rheumatic infection, such as carditis. Occasionally a strepto-

coccal infection will give rise to this odd allergic response, but not apparently the streptococcus responsible for rheumatism. Every case of this syndrome should therefore have a chest x-ray and a Mantoux test. It is common to find some enlargement of the hilar glands but it may be helpful to have a tomograph view in order to define the extent of these glands more exactly. As the condition is the presumed result of the patient's sensitivity to the protein of the tubercle bacillus, it is a wise precaution in performing the Mantoux test to do so with a weak solution and not more than 1 in 10,000 old tuberculin should be used in the first instance. Even this strength is liable to cause a severe local reaction at the site of the injection.

Phlyctenular conjunctivitis.—It is difficult to determine exactly how common this condition is, for these children tend to present at the eye clinics. It is not common but should immediately arouse suspicion of a tuberculous infection.

It will readily be appreciated that the foregoing is only a very brief description of tuberculosis as met with in childhood, but if it enables the practitioner and others to be alerted to the possibilities it will serve its purpose. For more detailed descriptions the reader is referred to the many excellent articles already available elsewhere.

CHEMOTHERAPY

Still pursuing the line that the practitioner must interest himself in preventive therapeutics rather than wait for the established disease, let us now consider the methods by which, to take an example, a two-year-old with a contact history and positive tuberculin test and radiological evidence of an uncomplicated primary complex might be treated. The first point to stress is the absolute necessity of always using at least two of the antituberculous drugs in combination. This must be done if the risk of producing a resistant strain is to be avoided. It is customary, though not invariable, to reserve streptomycin for the active case with evidence of lung involvement, and in the case of meningitis all the available therapeutic measures should be employed.

Isoniazid and PAS.—The combination of choice is isoniazid and para-aminosalicylic acid (PAS). These must be taken regularly for a minimum period of eighteen months and possibly for two years. Although some would argue that a year might be sufficient, most of us would like to have our own children treated for the longer time. Both drugs do occasionally give rise to side-effects but these are not as a rule of great moment, with the exception that PAS does cause nausea and sometimes sickness in a few cases. Moreover PAS is often prescribed in capsule form which may make its administration difficult in small children. This may be overcome by the use of a combination of these drugs of which there are now several preparations available. If the two drugs are combined, however, it is important to see that the dosage of each is adequate. The dose of isoniazid recommended is

5 to 10 mg. per pound (11 to 22 mg. per kg.) body weight per day, and of PAS 0.2 g. per pound (0.5 g. per kg.) body weight per day. Larger doses of isoniazid are now being used and seem to be safe and effective, and many children can thus avoid the use of intramuscular streptomycin.

It is not always easy to ensure that children take their tablets regularly and the doctor must impress upon the parents the absolute necessity for this and if need be enlist the help of a home visitor to supervise. Too large a supply should not be prescribed, in order that the parents may come back at regular intervals to have the child seen and questioned about drug administration. The urine may be tested for PAS excretion as a further check. This is done by adding six drops of urine (0.1 ml.) to a mixture of one dro p of 3 per cent. ferric chloride diluted with 5 ml. of water. A positive reaction produces a distinct violet coloration; if negative there is no colour change although there may be some opalescence.

Streptomycin.—In the event of extensive active disease, streptomycin may be given in addition. It is difficult to say how long this will be needed as it will depend to some extent upon the severity and activity of the infection in each case, but six months would seem to be a minimum period. In such cases streptomycin is given by intramuscular injection once a day in doses of 20 mg. per pound (44 mg. per kg.) body weight per day with 0.5 to 1 g. as a maximal dose. Most children over the age of two years will need 1 g. a day, especially those with meningitis. The days of intrathecal injection of streptomycin for tuberculous meningitis are happily over, although it may be justifiable for a short time in the severe case.

Steroid therapy which was once thought to be contraindicated in this disease has a useful place under certain conditions, but it should be confined to hospital cases where the necessary supervision is available.

BCG VACCINATION

After many years of world experiment and trial, it now seems clearly established that BCG vaccine is an effective and safe preventive measure. There are isolated cases reported of generalized infection following vaccination, but these are so rare that they do not invalidate its general use. The present preparation of the freeze-dried vaccine seems safe and efficacious. Local reactions tend to occur only occasionally and are mainly due to faulty technique in the quite difficult intradermal injection, especially in the newborn. The optimum site for injection is over the insertion of the deltoid and the injection must be into the skin and not subcutaneously. Should gland infection follow, now happily much less common with the freeze-dried vaccine, it is usually quite benign though sometimes annoyingly resistant to treatment. If the injection is given too high up in the arm it may lead to enlargement of the supraclavicular glands which, if they should break down, might leave a visible scar. The thigh is not a suitable site for injection because of the risk of secondary infection, especially during the napkin years.

Resistant sores at the injection site usually heal with simple dressing, but breaking-down glands should be treated by streptomycin, 100,000 units per ml., after aspiration of the tuberculous pus.

It is now accepted that BCG should be given to any child at risk, i.e. to all child contacts with a negative tuberculin reaction. Ideally it is wise to isolate such children for six weeks after their last contact and then to repeat the tuberculin test, but in practice this is not often possible. If BCG does nothing else it at least affords protection against the dreaded tuberculous meningitis and miliary disease. In those countries where tuberculosis is endemic and living standards are low, campaigns to give BCG to all children, particularly the newborn, are being successfully carried out. In our country there is a case for only giving BCG to those individuals or communities at risk. The latter includes the adolescent, more especially the girls. It is now our practice to offer BCG to all negative tuberculin school-leavers, and local authorities through their school medical service are performing routine tuberculin tests on all these children. New-born babies whose mothers or household contacts are known or suspected cases of tuberculosis must be vaccinated. There is a case for offering all newborn the vaccine irrespective of contact history, and in those areas where tuberculosis is at all common this is becoming a routine practice.

Dosage.—The dose required is 0.1 ml. given intradermally. This is sometimes divided into two injections of half this amount, to lessen the risk of local breakdown, but with the new freeze-dried preparation this is not so necessary. The giving of an intradermal injection is not easy in the newborn whose skin is so thin, and it is perhaps advisable to become practised in the intradermal Mantoux test on older children first.

SOCIAL CONDITIONS

Tuberculosis will not be eradicated, which is our ultimate aim, until social conditions are improved. We have gone a long way in this country to prevent overcrowding, and child nutrition is at a higher standard than it has ever been. This unhappily is far from true of many countries in the world, and until their economic and social status is increased this disease will remain the scourge it still is, in spite of medical treatment and preventive vaccination.

CONCLUSION

This article has attempted to give a brief and simple review of the problems of childhood tuberculosis as the present-day doctor in this country may see it, and to give some guidance to the practising doctor on how he may best protect his child patients from the disease. It is indeed an encouraging thing that today one may write in this vein about a disease which has, until recent years, caused so much suffering and mortality in childhood.

RENAL DISEASE IN CHILDHOOD

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THE high incidence of renal disorders in early life, notably congenital malformations, pyelonephritis and nephritis, renders urinalysis essential in the routine examination of every sick child. Only if this is done can many kidney-destroying lesions be diagnosed early and the correct therapy employed.

CONGENITAL ABNORMALITIES

Congenital malformations of the urinary tract are found in about 10 per cent. of necropsies in children. Those which interfere with urinary flow are of serious import, for stasis encourages infection and obstruction causes back pressure on the kidney, producing hydronephrosis and progressive renal failure. Obstructive lesions occur twice as often above the bladder as below it. Posterior urethral valves, occurring almost exclusively in boys, may obstruct the urinary outflow. The finding of an enlarged bladder after micturition should arouse suspicion, for diagnosis and correction of this abnormality are of vital importance. In some cases of bladder dilatation with hydronephrosis no obstructive lesion can be found and it is postulated that there must be some underlying neuromuscular incoordination.

Partial obstruction of the ureters may be caused by a congenital malformation, compression by fibrous bands or by an aberrant blood vessel. There may be no symptoms referable to the urinary tract but many children do give a history of vague or even severe colicky abdominal pain. If on examination the kidneys appear enlarged or if abnormal elements are found in the urine the diagnosis should be suspected and pyelography be carried out. When there is obstruction to both kidneys from an early age progressive renal failure develops. The child presents the picture of chronic uræmia: failure to thrive, dwarfed and emaciated, and not infrequently with bony changes, often described as renal rickets. Only early diagnosis and surgical relief of any obstruction can prevent death occurring in a few years.

Congenital polycystic kidneys may produce much the same clinical picture. The condition is generally bilateral and often familial. Symptomatic treatment is all that can be offered to these unfortunate subjects.

PYELONEPHRITIS

Kidney infections are common in pædiatric practice. They are seldom limited to a single portion of the organ, hence the term 'pyelitis' is less applicable than 'pyelonephritis'. In the acute phase it can generally be controlled, but once the attacks become chronic or recurrent the treatment may be difficult and unsatisfactory.

Etiology.—The greatest incidence is in the first two years of life and is six times as common in girls as in boys except during the neonatal period,

when the sex incidence is about equal. *Escherichia coli* is the responsible organism in 80 per cent. of cases. Obstruction to the urinary flow is the most common factor in the production of chronic or recurrent infection and should always be considered when acute pyelonephritis, adequately treated, does not clear within three weeks or when the condition recurs.

Pathology.—In those cases which come to necropsy the infection is seldom limited to the renal pelvis alone, but is found distributed irregularly throughout the kidney mass. In the severe forms miliary abscesses may be found throughout the parenchyma and the kidney may be greatly swollen. With prolonged infection, extensive areas of scarring may be found. In most cases some degree of inflammation is found in the lower urinary tract and it is inflammation of the bladder which gives rise to symptoms, such as frequency of micturition, suprapubic pain, and dysuria.

Clinical manifestations.—(1) *In infancy* the onset is abrupt, with the temperature often reaching 103° to 104° F. (39.5° to 40°C.) but rarely sustained at this level for more than a day or two. Characteristically there are wide fluctuations with absence of fever for a day or so at a time. There are no localizing symptoms to indicate that the infection is in the urinary tract. When an ill baby presents with inexplicable vomiting, refusal to feed, or is not gaining weight adequately, the diagnosis of pyelonephritis should always be considered. Vomiting may be so striking and projectile in nature as to suggest a diagnosis of pyloric stenosis. Diarrhœa is less common but may occur as with other parenteral infections in early life. It must be emphasized that in some cases there is very little fever and the only symptoms are failure to gain weight and anorexia. The urine should be examined for pus in all such cases.

(2) *In older children* localizing signs and symptoms are often present. Owing to associated cystitis, frequency of micturition, urgency and dysuria occur and there may be pain localized to the renal area on one or both sides, with tenderness on palpation. Once again it must be emphasized that at any age symptoms referable to the urinary tract may be lacking and the diagnosis can only be established by examination of the urine. In most cases there is fever lasting seven to ten days before returning to normal. The acute clinical manifestations seldom last for more than three or four days, but the urinary changes generally persist for about three weeks. In chronic cases the infection may persist for months or years and be associated with intermittent fever, pyuria, and progressive renal destruction.

Diagnosis is based upon the demonstration of pus and bacteria in the urine although the diagnosis may be suspected from the signs and symptoms already outlined. The urine may be grossly cloudy but is usually clear. There are no satisfactory chemical tests for the presence of pus and the ultimate diagnosis depends upon microscopy. As a screening test the urine should be examined fresh, uncentrifuged, a drop being placed under a cover slip and the number of white cells in a field counted, using the low objective. If this exceeds five a urinary-tract infection should be suspected. The most

common source of pus in the urine from girls is from vaginal secretions and a catheter specimen of urine should be obtained if over ten pus cells are found per field in the ordinary specimen.

TREATMENT OF PYELONEPHRITIS

The majority of cases improve rapidly when the child is put to bed, kept warm, and given copious fluids. Sulphonamide therapy should be started at once but changed if the sensitivity tests indicate that it is not likely to be effective against the causal organism. Sulphadimidine is an active sulphonamide which gives satisfactory blood concentrations when given six-hourly. Toxic effects are rare and it is relatively soluble even in acid urine. Between the ages of 1 month and 3 months, 0.25 g. may be prescribed eight-hourly; from 3 months to 2 years, 0.25 g. six-hourly, and between the ages of 2 years and 5 years, 0.5 g. six-hourly. After the age of 5 years the dose may be proportionately increased from 0.5 g. to 1 g. six-hourly. Treatment should be continued for a minimum of fourteen days and there is some evidence that recurrence is less likely when it is continued for three weeks. It has been shown that a mixture of sulphonamides is less likely to produce deposits of crystals in the urine than most single sulphonamides given in equivalent dosage, but it is doubtful if such preparations have much advantage over sulphadimidine. If the patient has not made a complete recovery in three weeks or should the condition recur, the child should be admitted to hospital.

NEPHRITIS

Classifications of nephritis of increasing complexity have been produced year by year, but with no general acceptance. Ellis (1942) appeared to have clarified the existing situation and most clinicians welcomed his simplified scheme with relief. He regarded nephritis as being divisible into two clearly defined types, differing in etiology, pathology, clinical features, and prognosis. He referred to these as types I and II, corresponding respectively to the acute hæmorrhagic nephritis and nephrotic nephritis of earlier classifications. Many cases in childhood do not fit into either group clinically (Enticknap and Joiner, 1953; Clark, 1956) and it is now evident that the histological features which were thought to be typical of the two types are not as distinct as Ellis believed. The result has been a tendency for the terms 'acute hæmorrhagic nephritis', 'glomerulonephritis', and the 'nephrotic syndrome' to be re-employed.

ACUTE HÆMORRHAGIC NEPHRITIS

This is the most common form in childhood. Its true incidence is not known, for many mild cases are not diagnosed. Sixty per cent. of cases occur in patients under 21 years of age, the majority of whom are under the age of 7 years. An acute upper-respiratory infection precedes the nephritis by one to three weeks in 80 per cent. of cases. Epidemics of acute nephritis associated with *Streptococcus pyogenes*, type 12, have recently been reported (George *et al.*, 1958) and it has long been known that scarlet fever is compli-

cated by nephritis in 1 per cent. of cases. Staphylococci, pneumococci, and viruses have been implicated on occasion (Bates *et al.*, 1957). Both kidneys are invariably involved. In the acute phase there is a diminished glomerular filtration rate and consequently the filtrate passes through the tubules more slowly than normally, allowing a more complete reabsorption of sodium than usual and it is probably this which causes the water retention, cardiac enlargement, and general, pulmonary and cerebral œdema (Rosenheim, 1951). When diuresis occurs these signs and symptoms disappear rapidly.

Clinical manifestations.—There is considerable variability in the clinical pattern. The disease may show itself by slight malaise associated with hæmaturia which lasts a few days while the albuminuria clears within a few weeks. In more severe cases there may be an abrupt onset, with malaise and swelling of the face and feet. The urine may be dark with blood and frequently reduced in volume. The temperature may be within normal limits but is often raised to 103° to 104° F. (39.5° to 40° C.) for a few days before returning to normal, or it may fluctuate between normal and 100° F. (37.3° C.) for several weeks, indicating continued activity of the disorder. Vomiting is frequent at this stage and the child may complain of backache and abdominal pain. In 60 per cent. of cases there is slight hypertension but occasionally this may be very marked. The danger of hypertensive encephalopathy is then present. Diuresis generally occurs within three or four days of the onset and much weight may be lost even when there has been no obvious œdema. During the second week the constitutional symptoms disappear, the blood pressure returns to normal, and the urine ceases to be discoloured. Red blood cells and casts can still be found when a drop of urine is examined under the low power of the microscope and it takes six weeks on an average for all abnormal elements, including albumin, to disappear. Using a more delicate test, such as the Addis count, abnormal numbers of red cells may be found in the urine for many months, even when the patient is clinically well. Complete recovery may ensue but chronic nephritis may develop. The main difficulty in diagnosis lies in distinguishing acute nephritis from other conditions which produce hæmaturia, such as acute pyelonephritis, sulphonamide intoxication, or surgical disorders of the renal tract.

TREATMENT AND PROGNOSIS

Treatment is still largely empirical. The child should be confined to bed as soon as the diagnosis has been made. Daily examination of the urine should be carried out and the total volume of urine passed in each twenty-four hours recorded and also the degree of hæmaturia and albuminuria. The temperature, pulse rate, blood pressure, and the erythrocyte sedimentation rate (E.S.R.) should also be noted. It is my practice to treat all cases with penicillin orally unless vomiting is marked, when the intramuscular route is preferred. This treatment is continued for at least three weeks. In the acute phase of the illness the child seldom has a large appetite and a light diet is ordered, but as soon as his appetite returns a full diet can safely be

prescribed, there being no evidence that protein restriction is in any way beneficial (Illingworth *et al.*, 1954). Should there be marked oliguria or anuria the problem is quite different and the patient should be admitted to hospital as soon as possible. Fruit juices which contain large quantities of potassium are best avoided in the early days of the disease. The patient should be kept at rest until the constitutional symptoms have subsided, the blood pressure and E.S.R. have returned to normal, and the urine is free of cells, casts, and albumin. The minimum time for rest is six weeks.

Prognosis.—There are conflicting views on the prognosis of nephritis in childhood. The mortality rate in the acute phase is now of the order of 3 to 4 per cent. and the deaths are mainly from circulatory failure due to hyperpotassæmia. Antibiotics have removed the danger of acute complicating infections. Most of the long-term studies of nephritis in childhood report complete recovery in from 70 to 97 per cent. of survivors of the acute phase. On the other hand, some workers (Payne and Illingworth, 1940) have found evidence of active or latent nephritis in 70 per cent. of cases followed from one to twelve years after the acute attack. More recently, Clark (1956) has assessed the recovery rate of 178 children followed one to thirteen years after the onset of the nephritis as being of the order of 75 per cent.

THE NEPHROTIC SYNDROME

It is generally considered that patients with the nephrotic syndrome are suffering from albuminuric hypoproteinæmia of sufficient severity to cause œdema. Occasionally it is associated with renal vein thrombosis, congestion secondary to constrictive pericarditis, amyloidosis, lupus erythematosus, syphilis, x-ray damage to the kidney, and drugs such as troxidone or mercurial diuretics, but in the vast majority of cases in childhood no underlying cause is apparent. Some authorities consider these patients to be suffering from a form of glomerulonephritis (Janeway, 1957), whilst others consider them to have true nephrosis (Arneil, 1956). Severe prolonged proteinuria is the cause of the syndrome. It produces hypoalbuminæmia and consequently a fall in the colloid osmotic pressure of the plasma. Other low molecular weight proteins are lost in the urine and a low serum level of gamma globulin probably accounts for the tendency for these children to develop infections. Serum levels of the larger proteins, e.g. the α_2 globulins, β-lipoproteins and fibrinogen, may be raised. As a result the erythrocyte sedimentation rate is invariably raised in the nephrotic syndrome and is of no value in detecting superadded infection (Squire, 1953). The plasma volume may be greatly reduced in patients with nephrotic œdema and the blood volume is often 80 per cent. of normal values; it is thought that this may be the stimulus leading the adrenals to produce more of the salt-retaining hormone, aldosterone, which increases tubular reabsorption of sodium and thus produces further œdema.

Clinical manifestations.—The syndrome is seen most often in the first two years of life. Generalized œdema is almost invariably the first sign of

the disorder and varies considerably in degree from week to week. Albuminuria is always present. Hypertension is rare in the early stages. In cases proceeding to recovery, after weeks or months a diuresis occurs and there is a gradual return of the blood chemistry and urine to normal. Before the advent of antibiotics these patients were very liable to develop infections, particularly with the pneumococcus. The recovery rate is of the order of 40 per cent. without treatment and generally occurs within three years of the onset. The remainder progress to renal failure, often years later.

TREATMENT OF THE NEPHROTIC SYNDROME

This is largely symptomatic and aims at the prevention and control of infections, establishment of good nutrition, and control of œdema. In the acute stage the patient should be kept in bed. When the œdema has subsided the child should be allowed up. When acute infections occur they should be promptly treated with the appropriate antibiotics. The diet should be well balanced, containing plenty of protein, but salt should be restricted to less than 1 gramme a day. Many methods have been employed in an attempt to overcome the œdema but unless the proteinuria is permanently abolished the symptoms inevitably recur. A recent report (Lange and Wasserman, 1958) of 46 cases—35 children and 11 adults—who were treated with aqueous corticotrophin for at least twelve days and then with oral cortisone for three days in each week for a year, regardless of clinical or chemical improvement, is encouraging. Compared with a control series the mortality rate was greatly reduced and most of the children grew and behaved normally.

Prednisolone appears to be more effective than either cortisone or other steroids (Arneil, 1958). It may be used in a dosage of 60 mg. daily for ten days, then 40 mg. for ten days, followed by 20 mg. for ten days, then 10 mg. for a further ten days, or it may be administered intermittently three days in each week in a dosage of 60 mg. daily, but reducing the dosage by steps after several months to 20 mg. daily. Such treatment may be continued for months without serious side-effects. In spite of the expense it is clearly justifiable to offer this treatment to all children with the nephrotic syndrome.

NEOPLASMS IN THE KIDNEY REGION

Every solid mass in the abdomen of an infant or child should be regarded as a malignant tumour. Apart from secondary deposits, only two occur with any frequency in childhood: Wilm's embryoma and neuroblastoma arising from the adrenal medulla or from the sympathetic chain in that area.

Wilm's embryoma contains a variety of embryonic tissues and hæmorrhage often occurs into its substance. It is found seven times more frequently in boys than girls and generally presents before the age of five years. The first symptom is generally abdominal enlargement and on examination a large painless mass is felt in the loin. An intravenous pyelogram should be carried out in order to demonstrate a functioning kidney on the contralateral side before proceeding to operative removal of the tumour. With early

diagnosis and adequate surgery a 50 per cent. recovery rate has been reported.

Neuroblastomas occur mostly in the first three years of life and present in much the same way as a Wilm's tumour, but metastases are common and symptoms due to these may occur early. Operation and x-ray therapy offer the best chance of cure but the outlook is grave in all cases.

METABOLIC DISORDERS

Renal acidosis.—This condition commonly presents in the first few months of life after a period of apparent good health, with anorexia, vomiting, constipation, failure to gain weight, and hypotonia. The urine is generally found to be alkaline and the plasma bicarbonate decreased to less than 40 vol. CO_2 per 100 ml. The condition is due to the kidneys failing to regulate the acid-base balance of the body by excreting a sufficiently acid urine (Doxiadis, 1952). It is treated by the administration of a mixture of 10 per cent. sodium citrate and 6 per cent. citric acid, 60 ml. per day in 4 to 5 doses, the dose being increased by 15 ml. at five-day intervals until the plasma bicarbonate reaches 45 vol. CO_2 per 100 ml. Although clinical improvement may be slow the treatment should be persevered with, as many babies die unless the necessary treatment is given. After several months the disorder corrects itself and complete recovery generally ensues.

Idiopathic infantile hypercalcæmia may simulate renal acidosis but is associated with a raised serum calcium (between 12 and 18 mg. per 100 ml.). The etiology is not known although some workers have suspected a hypersensitivity to vitamin D. Mild cases respond dramatically to a low-calcium diet and after several months can take a normal diet without recurrence of symptoms or hypercalcæmia. A more severe form of the disorder is recognized in which the baby's progress is unsatisfactory even when the biochemistry has been converted to normal. Marked hypertension, osteosclerosis, mental retardation, and a systolic heart murmur may be encountered. The appearance may be elfin-like, with pinched nose, nostrils pointing forward, the upper lip being prominent and loose. The mouth is sometimes asymmetrical and kept open (Joseph, 1958). It is possible that the poor prognosis may be improved with earlier diagnosis and the institution of the low-calcium regime.

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THE CŒLIAC SYNDROME

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The name 'The Cœliac Disease' was given in 1888 by Dr. Samuel Gee of St. Bartholomew's Hospital to an important group of disorders in children and adults, the main features of which were recurrent diarrhœa with bulky pale stools, abdominal distension, severe wasting, pallor and arrested growth. For many years the condition was regarded as a clinical entity, although it was described under various names, such as chronic intestinal indigestion and acholia. The passage of time and advances in medicine have seen the differentiation of four major diseases from the syndrome, namely, abdominal tuberculosis with steatorrhœa, chronic *Giardia lamblia* infestation, cystic fibrosis of the pancreas and classical cœliac disease. These conditions will now be considered in the order of their differentiation.

ABDOMINAL TUBERCULOSIS

With improvements in the clinical diagnosis of abdominal tuberculosis in the early years of this century, particularly the introduction of reliable specific skin tests such as the Mantoux reaction, the separation of the occasional case in which steatorrhœa developed owing to extensive involvement of the intestinal wall by the tuberculous process presented little difficulty. Happily, all forms of abdominal tuberculosis are now extremely rare in Great Britain, thanks to the virtual elimination of bovine tuberculosis from our dairy herds.

GIARDIASIS

It has been known since the 1880's that the flagellated intestinal protozoan *Giardia lamblia*, which is found in all parts of the world though most commonly in the tropics, is sometimes pathogenic. Much has been written in the present century on the clinical features of this infestation, chiefly in the Latin countries. It is very common in children and less so in adults, yet few systematic observations were made on children until the Hungarian pædiatrician, Véghelyi, published the results of a controlled study of a large series of infested children in 1938.

In this condition enormous numbers of these organisms in the vegetative stage adhere to the epithelial cells of the duodenum and upper jejunum, and Véghelyi found symptoms of disease in three-quarters of those infested. Acute or subacute enteritis is usually the first symptom and this is sometimes followed by a recurrent or chronic illness the principal features of which are anorexia, recurrent vague abdominal pain, intermittent and variable diarrhœa, lassitude, dizziness, frequent headaches, loss of weight and anæmia. In the rare heavily infested cases, with much diminution of

the absorptive surface of the upper bowel, features characteristic of the cœliac syndrome may also develop, notably steatorrhœa and abdominal distension.

The thick-walled oval cysts of *Giardia lamblia*, measuring 8 to 12 microns in length and containing 4 nuclei, are usually abundant in the fæces, and the vegetative form also occurs during exacerbations of diarrhœa. Diagnosis depends upon finding the organism in fresh stools, a technique which is not difficult. Treatment has been dramatically successful in recent years since the introduction of mepacrine hydrochloride which is given in doses of up to 0.1 g. thrice daily for five days. Such a course of therapy, which seldom needs to be repeated, promptly alleviates the symptoms and there is a rapid improvement in health with a good gain in weight and disappearance of the anæmia.

Fortunately, frank disease due to giardiasis is seldom encountered in this country, although outbreaks affecting a high proportion of children and staff in residential nurseries have been recorded (Ormiston *et al.*, 1942).

Severe untreated *ascariasis*, as seen occasionally in the tropics, may also be a cause of the cœliac syndrome.

CYSTIC FIBROSIS OF THE PANCREAS

This common disease, with an estimated incidence of 1 in 1000 live births, may be said to have entered the medical arena when Dorothy Andersen (1938), of the Babies' Hospital, Columbia Medical School, New York, read a report of her clinical and pathological study on 'Cystic fibrosis of the pancreas and its relation to cœliac disease' at a joint meeting of the American Pædiatric Society and the Society for Pædiatric Research. This report gave the first comprehensive account of the disease, which time has proved to be remarkably complete. The stimulus to research and the dissemination of knowledge about the disease which followed this notable event soon enabled it to be diagnosed with increasing frequency. Dr. Andersen analysed the clinical and pathological features of the disease in 49 cases, 20 from the records of her own hospital, 2 by permission of pædiatric colleagues and 27 adequately authenticated cases from the world literature—20 being collected from the literature on cœliac disease and pancreatic insufficiency and 7 from the literature on vitamin A deficiency. In several of these published cases, most of which had been reported in German and American journals, the authors had not clarified the features of the clinical entity described by Andersen, in spite of observing gross histological changes in the pancreas, and had regarded the cases as being examples of either cœliac disease or vitamin A deficiency.

In 1919, Passini of Vienna, in a paper on 'Diseases of the pancreas as a cause of failure to thrive in children', mentioned two cases in siblings with characteristic pancreatic lesions. Although he gave few clinical details both cases showed the principal features of cystic fibrosis of the pancreas. The

first gained little weight, had loose, bulky, fatty stools and died of broncho-pneumonia at nine months. The second remained at its birth weight and died at two months of broncho-pneumonia and empyema. The assumption of pancreatic disease was confirmed at necropsy, both having a shrunken pancreas of half the normal size with cystic degeneration. Passini concluded that gross pancreatic hypofunction was the probable cause of the failure to thrive. Clarke and Hadfield, of Bristol, gave a more detailed clinical and pathological description of the disease in a child who died of broncho-pneumonia at four years in 1924. It is probable that two of the other five children in the family who died of pneumonia at 2½ months also had the disease. They stated that 'several points in the history and physical condition suggested a diagnosis of cœliac disease, in itself an obscure complaint, but this diagnosis, untenable on closer clinical observation, was definitely excluded by the post-mortem examination'. Among the few who regarded their cases as being examples of a disease entity, Margaret Harper, of Melbourne, and Parmelee, of Chicago, deserve special mention. The former described two cases in 1930 and her conviction of the importance of the disease, and her persistent interest in it, enabled her to report eight more in 1938, along with a description of the salient features of the condition and its differentiation from cœliac disease. Parmelee, who recorded two cases in 1935, stressed the fact that this disease has a symptomatology and a clinical course quite different from those of cœliac disease.

More recently, well-illustrated monographs have been published by Bodian (1952) of The Hospital for Sick Children, Great Ormond Street, and May (1954) of Iowa. Little of importance has been added since then, apart from the additional diagnostic tests to which I shall refer later.

CLINICAL AND PATHOLOGICAL FEATURES

As first pointed out by Andersen in her classical paper there are three clinical types of this disease each occurring in a definite age-group:—

(1) Meconium ileus—during fœtal life or the first week of life.

(2) Failure to thrive and bronchitis—during the first year.

(3) 'Cœliac syndrome'—after the first year.

There is often no clear distinction between the second and third types.

Meconium ileus.—This is the most severe form of the disease. Its early manifestation is caused by the failure of inspissated meconium to pass into the colon and its accumulation in the small intestine with gross distension. This may cause perforation of the ileum and meconium peritonitis either before or after birth. That this may occur long before birth is proved by the occasional occurrence of calcification in the peritoneal exudate, such as was found in a new-born baby born with a distended abdomen who was under my care several years ago. This baby, the second in the family—the first having died of the disease in infancy—survived for only a few hours. Usually the disease is not diagnosed until a day or two after birth, when

suspicions are aroused by the failure to pass meconium, increasing abdominal distension and the onset of vomiting. A volvulus of the loaded ileum may occur within a few days causing strangulation of the intestine. Attempts have been made to evacuate the inspissated meconium surgically, with only occasional success.

Failure to thrive and bronchitis in infancy.—This is much the commonest manifestation of the disease. In most cases failure to thrive within the first few months begins to cause concern. There is a slow irregular gain in weight, in spite of a good appetite and adequate food intake, and modifications in the type of feeding have little beneficial effect. The stools usually do not attract attention in the early months, although their bulk is slightly increased. They then become looser, paler and foul smelling, particularly after the inception of mixed feeding. A tendency to recurrent respiratory-tract infection soon develops and is often the first abnormality noted. It usually becomes intractable within a few months. Many cases have a violent spasmodic type of cough which is often mistaken for whooping-cough. A predominance of the *Staphylococcus aureus* in the respiratory tract is a characteristic feature and, unfortunately, strains which are resistant to penicillin and several of the newer antibiotics often defeat attempts to suppress and control this dangerous form of bronchitis, with the result that subacute broncho-pneumonia and bronchiectasis often develop. Small abscesses tend to develop in staphylococcal pneumonia, and in some cases rupture of one or more of these into the pleural space occurs with the production of pyopneumothorax.

The importance of eliminating this disease as a possible cause of intractable bronchitis in infants who are failing to thrive cannot be overstressed. This implies admission to a pædiatric unit for the performance of laboratory tests which cannot be done at home. Unfortunately, even with early diagnosis and appropriate treatment a considerable proportion of infants with this type of the disease fail to survive for a year, although some may do so for several years.

Most cases in this group fail to thrive normally from birth, but occasionally the clinical course appears normal for several months before failure to thrive, abnormal stools and respiratory symptoms supervene. In the latter circumstances analysis of the duodenal juice shows a progressive diminution and eventual disappearance of pancreatic enzyme content.

A few years ago I saw a baby of seven months who had recently developed rather pale offensive stools, and slight respiratory-tract infection. He looked the picture of health with a normal weight of 17½ lb. (7.9 kg.) and it was tempting to regard the disturbances as transient, but the history of an elder sibling of 5 years having died of 'cœliac disease' and bronchiectasis at once aroused the suspicion of cystic fibrosis of the pancreas. Analysis of the duodenal juice revealed a low trypsin content repeatedly and the diagnosis of cystic fibrosis was confirmed. Failure to thrive and intractable staphylococcal respiratory infection complicated by pyopneumothorax followed and in spite of careful dietetic and anti-infective therapy the child died a few months later.

'Cœliac' type.—This group comprises the least severely affected cases. The appellation 'cœliac' type sometimes given to this group is unsuitable and misleading, for patients in this category bear only a superficial resemblance to classical cœliac disease. They may have thrived in infancy, like children with cœliac disease, but usually they have not. The points of resemblance are failure to thrive, abdominal enlargement and pale bulky stools, but

FIG. 1.—Radiograph of the chest in a patient, aged 14 years, with the 'cœliac syndrome,' showing areas of chronic pneumonia and localized obstructive emphysema. The large hilar shadows are probably mainly vascular and related to pulmonary hypertension.

unlike cœliac disease the appetite is voracious, the stools are extremely foul-smelling owing to an excess of undigested putrefying protein and there is usually chronic respiratory tract infection of the kind described in type 2. In most cases treatment is disappointing owing to the intractable nature of the respiratory infection and, although the rate of general deterioration can be slowed to a varying extent, the disease runs its inexorable course with progressive destruction of the lungs, clubbing of the fingers and toes and the development of cor pulmonale. Few survive to adult life. My oldest patient is a boy of 14 years who in spite of careful supervision has slowly developed the foregoing late features and is now unable to attend school (fig. 1).

The main difference between types 2 and 3 is largely one of degree. In the former the disease reaches a severe stage in infancy and the respiratory features overshadow the alimentary, whilst in the latter the alimentary features are of equal or even greater prominence, at any rate in the earlier stages.

PATHOGENESIS OF CYSTIC FIBROSIS OF THE PANCREAS

The tendency for the disease to occur in more than one sibling was observed by some of the early authors, and with further study this has been shown to be a common occurrence. Fibrocystic disease has been shown to be a hereditary disease transmitted by recessive genes with a familial incidence risk of 1 in 4. Some families are more unfortunate than this average incidence would suggest, for I have had several families with two affected children, often the only two, and recently one in which all three died of the condition aged 4 months, 5 years and $2\frac{1}{2}$ years, respectively.

The means by which the genetic trait determines the pathogenesis of the disease remains obscure and controversial. The most popular hypothesis, propounded by Wolbach (Blackfan and Wolbach, 1933) and extended by Farber in 1944, assigns the pathogenesis to a genetic aberration in the type of secretion elaborated by mucus glands throughout the body. The hypothesis is based upon the morphological appearance of secretions in the dilated pancreatic ducts and mucous glands and the viscid nature of secretions obtained from the respiratory system, intestine and biliary tract. The disease is thus envisaged as a systemic disorder affecting the pancreas, lungs, and liver particularly, because the obstructive effects of viscid mucus secretions would interfere seriously with the functioning of these organs. The authors of this hypothesis introduced the designation 'mucoviscidosis' which has gained wide currency, though it is not universally accepted.

DIAGNOSIS OF CYSTIC FIBROSIS OF THE PANCREAS

Familiarity with the characteristic features of the disease should arouse suspicion at a fairly early stage in most cases. With such a serious prognosis it is essential to prove or disprove the suspected diagnosis without delay. This entails admission to a pædiatric unit for general appraisal, also bacteriological investigation of the respiratory tract, radiological examination of the lungs, and analysis of the stools. Increased fæcal fat can easily be demonstrated by microscopic examination of diluted stool stained with Scharlach red. Quantitative chemical estimation of fat is unnecessary because determination of the ratio of neutral fat to fatty acids does not help to differentiate fibrocystic disease from cœliac disease, since neutral fat may be split by intestinal lipase in fibrocystic disease.

Several specific diagnostic tests have been developed and the performance of the more valuable of these is essential to place the diagnosis beyond doubt. The estimation of the amount of trypsin in the duodenal juice

obtained by intubation was, for some years, regarded as the only reliable test, but it often proved difficult to pass a duodenal tube and to obtain satisfactory specimens in infants and young children, several attempts sometimes being necessary. The methods of estimating the trypsin content of fresh stool by incubating an emulsion of it on the gelatin surface of an x-ray plate, and the performance of gelatin-tolerance tests to measure the rise of amino-nitrogen in the blood after the ingestion of a gelatin meal, though of some value, both proved too unreliable. The more recent discovery that the sodium chloride content of sweat is greatly increased in fibrocystic disease has proved of great value in diagnosis, for it is easier to obtain sweat than duodenal juice for analysis. The child is heated in a shock cage and sweat is collected by absorbent material and the chloride content is estimated in the biochemistry laboratory. A simpler method, useful for screening, is to apply the balls of the patient's fingers to the surface of an agar plate containing silver nitrate and potassium chromate. The density of the silver chloride precipitate in the finger imprints is proportional to the chloride content of the sweat and is strikingly increased in this disease (Shwachman and Gahm, 1956; MacFarlane *et al.*, 1957).

TREATMENT OF CYSTIC FIBROSIS OF THE PANCREAS

Careful management of children with this disease is very important, for appropriate replacement and anti-infective therapy can usually ameliorate the lot of the less severely affected and prolong life.

Pancreatin, given in powder form to young children and as granules to older children, should be given in large doses to supply the lacking pancreatic enzymes, also a high-protein diet to compensate for deficient digestion and absorption of protein. It is not necessary to give amino-acid preparations, formerly advocated, provided ample pancreatin is given. In severe cases the fat intake should be reduced.

Control of respiratory-tract infection, the main danger, is difficult because of the strong tendency for antibiotic-resistant strains of *Staphylococcus aureus* to emerge, particularly after prolonged treatment. Consequently it is necessary to be guided in one's choice of antibiotics by repeated bacteriological assessment of the degree of resistance of the particular strain of staphylococcus to the various antibiotic agents, choosing one to which there is little or no resistance. It is often necessary to advise long-term prophylactic therapy of the most appropriate antibiotic to prevent recurrent infection, or, more often, to restrain chronic infection.

CŒLIAC DISEASE

The nature of classical cœliac disease, the salient clinical features of which are well known, continued to baffle clinicians and pathologists until the present decade, when, in 1950, the Dutch pædiatrician, Dicke, reported that children with cœliac disease can be successfully treated with a diet free

from wheat and rye flour. It was soon established that wheat and rye starch are harmless and that the injurious substance must therefore reside in the protein fraction known as gluten (Anderson *et al.*, 1952; van de Kamer *et al.*, 1953). The latter showed the offending fraction of the gluten to be the polypeptide, gliadin. The efficacy of a gluten-free diet in cœliac disease in childhood was demonstrated by both these groups of workers.

This concept of the pathogenesis of cœliac disease, though not yet understood, has been generally confirmed by the uniformly successful results obtained with gluten-free diets. It explains why cœliac disease seldom develops until after the introduction of wheat and rye into the diet in later infancy. The specificity of the offending polypeptide in wheat and rye gluten is shown in cœliac patients by the harmlessness of maize, rice and probably also of oats, for these cereals contain other kinds of gluten. The harmful effect of wheat and rye gluten appears to be quantitative, but it has not yet been established what level of gluten intake is without effect in a gluten-intolerant individual. Cooke (1958) believes that there may be a 'constitutional enzymatic defect' which is rendered evident by gluten administration, and that this defect is probably situated in the epithelial cells of the intestine, for it is now believed that the metabolic functions of these cells outweigh their absorptive ones.

As soon as all other possible causes of the cœliac syndrome have been excluded in the manner described in this article, and a diagnosis of 'gluten-induced enteropathy' has been made, confirmation should be sought by instituting a gluten-free diet. Improvement in the patient's condition is not immediate and it is usually several weeks before there is a definite improvement, but this is continuous thereafter with a steady gain in weight, a resumption of growth and improved fat absorption with a return of normal stools. For effective therapy gluten intake must be kept down to a very low level, and it is therefore advisable to eliminate gluten as completely as possible. The intolerance appears to persist for a long time and it may prove necessary for a gluten-free regime to be continued indefinitely. For full details about this valuable new therapeutic and prophylactic regime, readers are referred to two excellent articles on gluten-free diets: by Miss Patricia Torrens in last month's issue of *The Practitioner* and by Dr. Fletcher and Miss McCririck (1958).

ADULT CŒLIAC DISEASE

The introduction of the gluten-free dietary regime has had more far-reaching effects than the successful treatment of cœliac disease in childhood, for it has helped to clarify some of the confusion about steatorrhœa in the adult. Non-tropical sprue, also known as idiopathic steatorrhœa, has been found to respond to a gluten-free diet in a similar manner to cœliac disease in childhood, whereas tropical sprue has not (van de Kamer *et al.*, 1953). In a recent study French *et al.* (1957) had clinical cures in 15 out of 22

patients with non-tropical sprue, and a rapid hæmatological remission was produced in these cases by the removal of gluten from the diet. This response to the gluten-free regime, as in cœliac disease in childhood, and the high incidence of previous cœliac disease in adults with non-tropical sprue, have convinced Cooke *et al.* (1953) that 'adult cœliac disease' is a more suitable term than either idiopathic steatorrhœa or non-tropical sprue for the patients in this group—the majority—who respond to a gluten-free diet. Like Thompson (1951) they believe that it is a familial constitutional disorder with an enzymatic defect, possibly in the intestinal cell. There is much to be said for Frazer's (1955) suggestion that 'gluten-induced enteropathy' might be used as an inclusive term applicable to all patients, regardless of age, in whom a demonstrable enteropathy can be shown to be caused by gluten.

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ENDOCRINE DISORDERS IN CHILDHOOD

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Our knowledge of endocrine disorders in childhood has expanded rapidly in the last decade, and we propose to restrict this article to three aspects of the subject in which major advances have been achieved: pituitary growth hormone, disorders of the thyroid, and sex differentiation.

PITUITARY GROWTH HORMONE

Isolation and characterization.—In 1939, van Dyke in his work on the pituitary gland stated that 'although there is general agreement that the pituitary among endocrine glands is the most important regulator of growth, it is not known whether this is effected by a specific growth-promoting hormone and no investigator has succeeded in preparing a satisfactorily purified growth-promoting extract of the pituitary body'. The first to report the isolation of a purified pituitary growth hormone (GH) were Li *et al.* (1945) who obtained it from ox pituitaries in 1944. In 1951, Raben and Westermeyer reported the isolation of an active, purified GH obtained as a by-product of the preparation of corticotrophin from fresh frozen pig pituitaries. The studies on the effects of purified GH which then followed indicated that growth hormones were to a certain extent species specific; GH from higher species were always effective in lower species, but the opposite never seemed to be true. The preliminary reports of Knobil *et al.* (1956) on the lack of response to beef growth hormone by normal and hypophysectomized monkeys suggested further that this species specificity might be the explanation for the generally noted ineffectiveness of non-primate GH in man.

It was not long before it became possible to test this thesis in a positive manner.

In 1956, Li and Papkoff and, in 1957, Raben reported methods for preparing pure primate GH. Raben found the yield from man and monkey pituitaries greater than that from pig by a factor of 2 to 3. Activity per unit weight of GH itself was very similar as measured in the rat. Knobil *et al.* (1957, 1958) provided final proof of the specificity of primate growth hormone by showing that hypophysectomized monkeys reacted to these preparations with all the expected metabolic changes and with a striking proliferation of the costochondral junction which characteristically atrophies in this species after hypophysectomy.

A partial explanation for the species specificity was offered by Li and Papkoff (1956), who published data on the composition and chemical properties of the different growth hormones.

They found beef GH to have a molecular weight of 42,600, to contain 396 amino-acids, and to have an isoelectric point of 6.85, as compared with that of man and monkey, with molecular weights of about 26,000, with only 245 and 241 amino-acids, respectively, and with an isoelectric point of 5.5. These findings were confirmed by Raben. Li and Papkoff further reported that digesting beef GH with chymotrypsin and trypsin to a degree sufficient to split off 24 to 30 per cent. of the molecule did not markedly affect the biological activity of the GH. No original GH molecules could be recovered from the digest after this partial hydrolysis.

They then postulated the existence of an identical or very similar 'active core' in all growth hormones, and suggested that the variation in the remaining part of the molecule might account for the species difference observed. It is to be hoped that a way may be found to isolate this active core without rendering it inactive biologically.

Metabolic studies.—Short- and long-term studies in man show that the metabolic effects of GH are essentially the same as those known from animal experiments. A marked retention of nitrogen and potassium occurs in proportions found in protoplasmic tissues. Calcium and phosphorus, as well as sodium, are retained. The urinary output of aldosterone is increased. Increase in weight and statural growth sets in and the serum inorganic phosphorus and alkaline phosphatase concentrations rise to levels characteristic of growing children.

GH also has striking effects on fat matabolism. Greenbaum and Glascock (1957) report that rats on GH therapy change their respiratory quotient from ordinary levels of 0.85-0.90 to 0.72, a figure characteristic of metabolism based entirely on fat. Engel *et al.* (1958) demonstrated a significant rise in serum unesterified fatty acids in rats after injection of GH, indicating a mobilization of peripheral fat stores. The conclusion seems to be that in order to establish positive nitrogen balance and hence growth, the organism has to drain heavily on other sources of energy, and mobilization of fat seems to be the most important way in which this is accomplished. Consequently, unless energy input is sustained at high levels, the increase in body protoplasm is accompanied by a marked decrease in body adipose tissue.

Diagnostic assays.—Until quite recently assays have been based mostly on the response of rats to test materials.

All these tests required much time (4 to 20 days) and were inaccurate and non-species specific. A new approach to this problem has been opened up by Read and Stone (1958) who succeeded in immunizing rabbits against human GH. Sera from these rabbits, when used in the tanned red blood cell system of Boyden, showed great specificity and sensitivity to human GH. In a later report, Hayashida and Li (1958), who also used sera from rabbits immunized against human GH, obtained a definitely positive precipitin test with as little as 0.1 microgram of GH.

Keele *et al.* (1958) report levels in normal children and adults as 0.16 to 0.64 micrograms per ml. of serum. In Keele's report the levels in infants and adults were lower than in children, thus recalling the interesting question of what besides GH regulates growth in the first year or two of life, and the well-known clinical observation that hypopituitary patients have a nearly normal growth rate until the age of two years.

CLINICAL USES

The prime indication for the clinical uses of human GH at present seems to be dwarfism due to anterior pituitary deficiency. In long-term treatment, Raben (1958) reports a growth rate of 2.5 inches (6.3 cm.) a year in a hypopituitary dwarf, treated for twenty months, as opposed to 0.5 inch (1.2 cm.) a year before therapy. The same GH preparation has also caused two of Henneman's (1958) hypopituitary patients to grow at the rate of 2.3 inches (5.8 cm.) and 2.6 inches (6.6 cm.) a year, respectively. The dose recommended by Raben is 2 mg. of human GH three times a week. No local reactions at the site of injection have been observed.

The chief source of human GH at present is human pituitaries obtained at necropsy.

According to Gemzell and Li (1958) and Gemzell and Heijkenskjöld (1956), the GH content of a single pituitary ranges between 2.7 and 6 mg. With the previously mentioned dosage, this means that about 60 to 75 pituitaries are needed to supply one patient for one year.

The collection of pituitaries can be made by any pathologist at necropsy. After removal they should be stored in acetone. The activity survives the delay between death and necropsy. The age of the donor individual seems unimportant; Gershberg (1957) has shown that the content of physiologically active GH per 100 micrograms of wet tissue or per gland is the same in pituitaries of individuals over 45 years of age, in a 12-year-old boy and an 8-month-old fœtus.

Although Beck *et al.* (1958), in short-term studies on human subjects, noted some 'diabetic' changes in the glucose-tolerance curves, none of Raben's or Henneman's patients on long-term intermittent therapy with 6 mg. GH a week has shown any disturbances in carbohydrate metabolism.

The growth-promoting action of GH on tumours seems well substantiated by the known effects of hypophysectomy and of GH application in experimental carcinogenesis (Gardner, 1953; Kirschbaum, 1956; Miraud and Hoffman, 1957). At least two patients with hypopituitarism due to craniopharyngioma have shown evidence of tumour growth while on GH therapy, and in one the hemianopsia improved slightly on discontinuing GH (Henneman, 1958). It therefore seems advisable at present to delay GH treatment of patients having any kind of tumour until more is known about the potential dangers involved.

CHRONIC LYMPHOCYTIC (HASHIMOTO'S) THYROIDITIS

This disease has been the focal point of a series of fascinating researches in recent years. In the course of carrying out studies designed to provide means of distinguishing between various types of chronic thyroiditis, Fromm *et al.*, in 1953, found elevated gamma globulin levels in four patients with Hashimoto's disease. Shortly afterwards, Luxton and Cooke (1956) observed that patients with this condition were apt to have abnormal serum protein flocculation reactions as measured by the zinc sulphate, thymol turbidity, cephalin flocculation and colloidal gold techniques. They observed, moreover, that these abnormalities gradually disappeared following surgical removal of the gland. These findings, coupled with the fact that

the thyroid in Hashimoto's struma characteristically is infiltrated with larger numbers of lymphocytes, which are thought by some to be antibody producing cells, led Roitt *et al.* (1956a) to postulate that all these changes might be due to an immune process directed against the thyroid gland. Shortly afterwards, they (Roitt *et al.*, 1956b) succeeded in demonstrating by means of an agar diffusion technique that sera from patients with Hashimoto's disease actually contained precipitating antibodies against human thyroglobulin: 109 of the first 144 patients tested had positive titres.

Meanwhile, Witebsky and his colleagues (Witebsky, 1957; Witebsky *et al.*, 1957a), who had been working independently on the same problem for a number of years, came to the same conclusion by a slightly different route.

They had become intrigued by the demonstration of Hektoen and his colleagues (1927) about 30 years previously of the fact that thyroglobulin had immunological properties. Using a system consisting of an antigen comprised of thyroglobulin mixed with Freund's adjuvant and an indicator based on the tanned cell hæmagglutinin method of Boyden, they were able to measure antibodies even in very low titre. With the aid of this technique it was possible to demonstrate that rabbits, guinea-pigs and dogs could be 'auto-immunized' against their own thyroglobulin. Moreover, it was found in hemithyroidectomized rabbits that sensitization with thyroglobulin extracted from the removed part of their own gland resulted also in damage to the remaining lobe. Histological examination of the remaining tissue showed widespread lymphocytic infiltration, damage and disappearance of thyroid follicles and evidence of increased thyroid stimulating hormone (TSH) action in the remaining thyroid cells: changes closely similar to those considered characteristic of Hashimoto's disease as observed clinically. Lastly, they, too, found that two-thirds of the 18 patients under their care had antibodies to thyroglobulin in their circulation (Witebsky *et al.*, 1957b).

It would appear therefore that auto-immunization may play a major role in the pathogenesis of chronic lymphocytic thyroiditis. Roitt and Doniach (1957) suggest that the process starts with an initial release of thyroglobulin from the follicles, by an as yet unknown mechanism. This is followed by an auto-immune response, which stimulates invasion of the gland by lymphoid elements with local antibody production. The antibody-antigen reaction is cytotoxic, causing damage to the epithelium of adjacent follicles. Further release of colloid follows and the destructive, self-perpetuating process continues. Applying fluorescein-labelled antibodies from the serum of a patient with Hashimoto's disease to slices of thyroid removed from the same patient, White (1957) showed localized fluorescence in the colloid of the follicles and also in streaks projecting out into the interfollicular spaces. A widening of the concept of auto-immunity in thyroid disease was suggested by the finding that certain patients with primary, non-goitrous myxœdema also showed the same antibodies as cases with Hashimoto's thyroiditis. Six out of 27 reported by Roitt and Doniach (1957), four out of 28 reported by Goudie *et al.* (1957), and three out of nine reported by Trotter *et al.* (1957) had positive results. In more recent series, using precipitation, hæmagglutination and complement fixation tests, Roitt and Doniach (1958) and Owen and Smart (1958) showed that about 80 per cent. of all patients with non-goitrous myxœdema have demonstrable antibodies. They differ from cases

of Hashimoto's disease in tending to have lower titres. By subdividing their cases of Hashimoto's thyroiditis into recent, untreated and long-standing or treated cases, Owen and Smart found such an agreement in distribution of titres between the last group and the non-goitrous myxœdema group as to suggest that Hashimoto's thyroiditis and non-goitrous myxœdema may represent two degrees of the same auto-immune process.

Following up Trotter's suggestion that more than one antibody is present, Roitt and Doniach (1958) have established the existence of another antibody. It can be detected by the complement fixation test and is easily separable from the thyroglobulin precipitin protein. As compared with thyroglobulin the antigen was found to be localized in the microsome fraction of thyroid homogenates. These complement-fixing antibodies are present in a number of cases of thyrotoxicosis, in which precipitin tests are always negative.

The finding of auto-immunity as a cause of thyroid disease invites active exploration of the possibility that other diseases of unknown etiology may be the result of auto-immunization to other body proteins.

CARCINOMA OF THE THYROID IN CHILDHOOD

In the last eight years reports on cancer of the thyroid in children and very young adults have been appearing with increasing frequency. The first to draw attention to a possible relation between the occurrence of cancer and previous exposure to radiation to the region of the neck, face and upper chest were Duffy and Fitzgerald in 1950. In 20 cases of thyroid cancer in childhood reported by these authors, 10 had received irradiation for 'enlargement of the thymus' in infancy. Clark (1955) reported that all of his 15 cases of thyroid cancer in patients under 15 years of age gave a history of radiation therapy to the region of the neck for benign conditions in infancy or childhood. Fetterman (1956) informed us that eight out of 10 cases had had irradiation to the face, neck or upper chest three to twelve years before cancer was diagnosed. In a recent report by Wilson *et al.* (1958) six patients irradiated in infancy for benign cutaneous lesions of the neck developed carcinoma of the thyroid gland. Crile (1958) published data on 18 children with carcinoma of the thyroid. Of the 14 cases from whom an adequate history could be obtained, 11 had had rœntgen radiation to the head, neck or thorax as infants, for benign conditions, including 'enlarged thymus'.

In an effort to gather controlled information Simpson and Hempelman (1957) have followed up 1,502 children known to have received radiation to the thymus as infants. In this group they found 10 cases of carcinoma and seven with adenomas of the thyroid. Only one adenoma and no carcinoma were found in 1,933 non-irradiated siblings. This report, correlating the site of radiation with subsequent tumour development, further substantiates the probability of a causative relation. The minimum dose observed to cause cancer was 180r in the first year of life in Simpson and Hempelman's group. Most of the patients had received 200r to 600r. Wilson states that as little as 130r given to an infant 2 months of age has been followed by malignancy.

The latent period differs in various groups, but is generally less than ten years in children irradiated in the first year of life, being somewhat longer in children irradiated after the first year.

Radiation as treatment of thyrotoxicosis was a widespread procedure about forty years ago. In the adult patients so treated the incidence of carcinoma was not significantly higher than in the general population. In 1949, Quimby and Werner surveyed by questionnaire several hundred patients who had received x-radiation to the thyroid and found only three cases of carcinoma. Thus the adult thyroid seems to be more resistant to the carcinogenic effects of irradiation than do the thyroids of infants and children.

With the easy availability and widespread use of radioactive iodine for diagnostic purposes this source of ionizing radiation has also to be considered. A diagnostic dose of 10 microcuries will deliver 25r to 30r to the gland, assuming even distribution in a 15-gramme thyroid and uptake of 50 per cent. With the reported minimum carcinogenic doses of 130r to 180r, and the known cumulative effect of radiation throughout life, it seems advisable to use I^{131} diagnostically in children only when very definite indications are present, and then to use the smallest dose possible. In our opinion (Arnold, Talbot and Cope, 1958), the use of radiation for control of thyrotoxicosis in infants and children is both undesirable and unnecessary.

SEX DIFFERENTIATION

In 1947, Jost succeeded in castrating male and female rabbit fœtuses at a time when the gonads were already histologically differentiated as testes or ovaries, but the differentiation of the genital organs had not yet begun. Allowed to proceed to term, all these fœtuses invariably developed as females. Unilateral removal of a testis led to development of a tube and uterine horn on the castrated side, but vas deferens and seminal vesicles were formed on the intact side, thus pointing to a specific local effect of the testis (Jost, 1950). Injection of androgenic steroids into pregnant animals resulted in partial masculinization of the external genitalia of the fœtus, but did not cause disappearance of the structures originating from the Müllerian duct (Jost, 1944).

Sex differentiation thus seems to occur in three distinct stages: (a) differentiation of the gonads, (b) differentiation of the genital ducts and (c) development of the external genitalia. The primitive gonads, identical in both sexes until the sixth week, develop either into testes around the seventh week or into ovaries around the tenth week. Each fœtus has Wolffian as well as Müllerian ducts and only the presence of a functioning fœtal testis at the critical time around the beginning of the third fœtal month will make the Müllerian duct degenerate and the Wolffian duct proceed to develop into epididymis, vas deferens and the seminal vesicles. In all other cases, independently of the presence or absence of an ovary, the development of the Müllerian duct will proceed along female lines, with disappearance of the structures of the Wolffian duct. Varying degree of development of the phallic

structure and fusion of the labio-scrotal folds in the midline determine the ultimate appearance of the external genitalia.

NUCLEAR CHROMATIN PATTERN

In 1950, Barr and Bertram discovered a difference in the pattern of nuclear chromatin in all resting somatic cells of the body: the presence in females of a conspicuous mass of heterochromatically staining chromatin near the inner surface of the nuclear membrane. These chromatic masses can be seen in biopsies of skin and in smears of oral and vaginal mucosa (Carpentier *et al.*, 1956; Marberger *et al.*, 1955; Moore *et al.*, 1953). There is also a definite difference in the polymorphonuclear leucocytes of the two sexes, in that they have a 'drum-stick' appearance in chromatin-positive cases (Davidson and Smith, 1954). The number of 'chromatin-positive' nuclei in the oral smears is less than 4 per cent. in genetic males and always over 20 per cent. in genetic females. For skin biopsies the corresponding numbers are 12 and 51 per cent., respectively. The accuracy of any selected technique is directly related to the competency of the individual doing the interpretation; in cases of doubt it is advisable to use more than one method.

Clinical use in the diagnosis of pseudohermaphroditism.—The genetic sex determination may be of great help in dealing with infants presenting with external genitalia of the 'imperfect male type'. If the nuclear chromatin pattern is of the female type, it is clear that the child is a genetic female who became exposed to abnormally large quantities of androgens during fœtal life. A common cause is congenital adrenocortical virilism, a condition which can be recognized by the presence of abnormally large amounts of 17-ketosteroids and of 17 to 20 diols in extracts of urine. Other causes are ovotestis and androgen or progestin therapy to the pregnant mother (Nellhaus, 1958; Wilkins *et al.*, 1958). In the latter conditions, the urinary output of steroids is normal for the age. If the nuclear pattern is of the male type, the chances are that the patient either has imperfectly developed testes or has a limitation in the capacity of his genital structures to respond to androgens (Grumbach *et al.*, 1955).

In addition, this index can be used as an aid in the diagnosis of gonadal dysgenesis in 'female' infants and children who are suspected of being cases of gonadal dysgenesis because they have webbing of the neck, are of short stature or have other characteristics of Turner's syndrome. Of Nelson's (1956) 103 patients with this malformation, 87 had the male type of chromatin pattern. Likewise, Grumbach found that 20 of his 22 patients were genetic males.

The fact that a child is genetically a male or a female does not mean necessarily that he should be reared in accordance with that finding. On the contrary, it usually is advisable to rear infants in accordance with their physical characteristics. In older children whose gender role has become firmly established, psychological as well as somatic factors must be taken into account.

TREATMENT OF IDIOPATHIC PRECOCIOUS PUBERTY IN GIRLS WITH PROGESTINS

Idiopathic or central precocious puberty is the most common cause of isosexual precocity in the female. With a good prognosis as to longevity and fertility it has the disadvantage of causing the child to be different from her contemporaries and therefore the subject of curiosity and to be subject to the risks of sex violation. Moreover, it results in premature closure of the epiphyses and hence short stature. In a preliminary report from this clinic, Richie and Crawford (1958) found that 1 to 3 mg. per day of 19-nor-17-ethinyltestosterone for one-and-a-half years given to an 18-month-old girl, and 50 to 75 mg. per day of ethinyltestosterone given for an equal period to a 5½-year-old girl, resulted in a striking diminution in the signs of œstrogen effect. Breast size diminished markedly and menstrual periods, which had been occurring regularly in the younger girl, were suppressed. Vaginal cytology showed disappearance of cornified cells and return to the precornified stage. In both cases the accelerated growth rate was reduced to levels normal for the age, but only in the older girl was this followed by a slowing of bone maturation; in the younger girl the bone age has continued to progress more rapidly than linear growth and chronological age. Temporary withdrawal of therapy resulted in prompt recurrence of the signs of precocity.

The available evidence (Elton and Edgren, 1958; Roch *et al.*, 1957) suggests that this type of agent acts more by blocking the effects of œstrogen at the end-organs than by suppressing gonadotrophin or œstrogen production.

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DIABETES MELLITUS IN CHILDHOOD

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ALTHOUGH diabetes mellitus commonly starts in the second half of life, no age is exempt and in 5 per cent. of patients the onset occurs within the first decade, whilst in about 12 per cent. the illness is present before the age of 20 years.

INCIDENCE

Henderson (1949) discovered 180 children suffering from diabetes mellitus in a total population of 767,000 schoolchildren between the ages of 5 and 15 years. If this incidence of 1 in 4000 to 5000 represents the frequency of the disease throughout England and Wales, there are approximately 1,500 children of school age suffering from diabetes mellitus.

There would be general agreement that inheritance plays an important role in the etiology of diabetes mellitus and the majority would support the view that it is transmitted as a non-sex-linked recessive. White (1941) reported a family incidence of 20 per cent. in her child patients at the time of the initial interview; this figure reached 50 per cent. after these children had been observed for fifteen years. There is no difference in the sex incidence during childhood and it is not until after the age of 40 years that the increased frequency in the female becomes apparent.

ETIOLOGY

The disturbance of carbohydrate metabolism which characterizes diabetes mellitus could result from a decreased production of insulin as the result of injury to the beta cells of the islets of Langerhans or from an abnormal destruction of insulin or a combination of both. Experimental diabetes mellitus has been produced by methods such as removal of the pancreas, the action of the pituitary, thyroid, adrenal and gonadal hormones, the administration of glucose in excessive quantities, the use of alloxan, certain chelating agents which remove zinc, and finally fluoroacetate (Danowski, 1957). These all produce their effect by reducing insulin production from the pancreas. Although in man diabetes is occasionally associated with disturbance in function of endocrine glands other than the pancreas, this is never a common occurrence. The small quantity of insulin which is required to obtain satisfactory control of the diabetes which follows pancreatectomy has always contrasted with the much larger amount needed to stabilize many of the patients with the naturally occurring disease. This discrepancy was responsible for focusing attention on the possibility that anti-insulin substances might prove to be important in the etiology of the spontaneous disease in man. During the past ten years, the existence of tissue enzymes which degrade insulin, 'insulinases', has been established. Their action appears to be opposed by insulinase inhibitors present in the liver and other

tissues. Mirsky (1956) has therefore suggested that diabetes mellitus may occur as the result of an excess of insulinases, a deficiency of anti-insulinases or both.

CLINICAL MANIFESTATIONS

The onset of diabetes mellitus is more abrupt in children than in adults and the duration of symptoms before medical advice is sought is measured in weeks rather than months. Thirst and polyuria are characteristic symptoms which are rarely absent. The polyuria may lead to nocturnal enuresis, and diabetes mellitus should always be considered as a possible explanation in the child who starts bed-wetting after an interval of good control. The appetite is variable but loss of weight soon becomes apparent and it is worthy of note that the diabetic child is commonly thin. Pallor, malaise and irritability are often present and skin irritation and infection are occasionally associated with diabetes. It is unusual for the child to be free from symptoms, but a routine urine examination may first raise suspicion of the disease. In a small and decreasing number of cases the diagnosis is only made after the onset of coma.

DIAGNOSIS

The recognition of diabetes mellitus would rarely present difficulty if every patient's urine were examined for sugar and, whenever a reducing substance was present, tests for acetonuria were carried out. Transient glycosuria is not uncommon in childhood and the presence of a reducing substance in the urine demands that a further two or three specimens be examined to establish that the finding was isolated. If a reducing substance is repeatedly detected, however, it must be identified and, if it is found to be glucose, a glucose-tolerance test is required. Only in this way is it possible to recognize those children whose renal threshold for glucose is lowered.

In children with diabetes mellitus there are usually large quantities of glucose in every specimen of urine and commonly there is an added ketonuria. These urinary findings in association with the symptoms already described make the diagnosis almost certain. Confirmation is obtained by estimating the blood-sugar level and in the presence of a marked ketosis this investigation should not be delayed. Provided the child's food intake has been normal and no carbohydrate has been taken in the previous two hours, a blood-sugar level of 200 mg. per cent. or higher establishes the diagnosis of diabetes mellitus. On those rare occasions when doubt still persists a glucose-tolerance test should be performed. The characteristic features of this investigation in diabetes mellitus are the abnormally high fasting blood-sugar level and after the ingestion of glucose the blood-sugar level rises farther and shows little or no fall even after two hours.

GENERAL TREATMENT

Diabetes mellitus is a permanent disability and great care is required to prevent the child being cast as an invalid. Both the parents and the patient should be instructed in the nature of the disease, for their intelligent coopera-

tion leads automatically to an improvement in the degree of control of the diabetes. The child's daily activities should approximate as closely as possible to those of his non-diabetic friends. Exercise should be encouraged and, in those children whose diabetes is well controlled, all forms of games should be allowed. Extra carbohydrate will be required following unusual exertion. The manifestations of hypoglycæmia should be described, practical instruction should be given in the measurement and administration of insulin and also tuition in the testing of the urine for sugar and ketones. The urine should be examined for sugar at least twice a day and for ketones weekly.

DIET

At the present time all would agree that the child's full food needs must be met. Originally a strict dietary regime was advised, with all articles of food being weighed. This regime failed to recognize that the child's appetite and activities are variable and its pursuance often produced emotional problems and active revolt. Stolte (1931) recommended a more liberal diet and this gradually increased in popularity when it became apparent that equally effective control was obtained by this method with greater cooperation from both parents and child. Although commonly referred to as a 'free' diet, it is more accurately described as a liberation from excessive restriction. The child's food should be comparable to that of the non-diabetic of the same age and similar to that offered to the other members of the family. Meals should be regular and he should not go for more than four hours without food. Sugar, jam and sweets need not be withheld but their consumption should be restricted and an attempt made to give comparable quantities each day.

Occasionally it is apparent that the family diet is unsatisfactory and in these circumstances weighing of the food should be advocated. The requirements for a child of a year are calculated as 1000 calories a day with an additional 100 calories daily for each subsequent year of life. The protein and fat are given in equal proportions with twice that quantity of carbohydrate. A quarter of the total diet should be given at each of the three meals, breakfast, lunch and dinner, and the final quarter divided to provide a snack for mid-morning, mid-afternoon and before retiring to bed.

INSULIN ADMINISTRATION

The severity of juvenile diabetes mellitus makes it imperative for insulin to be used, for in no other way can adequate control be ensured. There are several types of insulin which vary in their speed of action and the period in which they are effective (table I). The original soluble quick-acting insulin is the most suitable for initial stabilization. A convenient starting dose would be 5 units twice a day administered half an hour before the morning and evening meals. This quantity should be increased by 2 to 4 units each day ensuring that the morning dose remains some 4 or 5 units higher than the amount prescribed for the evening. When the urine becomes free from ketones and the glycosuria has decreased or is intermittent, an attempt should

be made to maintain stabilization with a single daily injection of insulin. Until recently this was usually obtained by using a combination of soluble and protamine zinc insulin. The latter substance contains an excess of protamine and if the two types of insulin are mixed in the one syringe or injected into exactly the same site, some soluble insulin will be converted into the protamine zinc form and interference with stabilization will follow. If only one syringe is used, soluble insulin should be introduced first and, after its injection, the point of the needle should be moved to another area before the protamine zinc preparation is administered. When giving the two types of insulin there should be a slight initial reduction in the total daily dosage, with about two-thirds of the requirements being administered as protamine zinc insulin and the remainder as soluble insulin.

Type of insulin	Effective range in hours		
	Onset	Peak	Cessation
Soluble	½	2	8
Protamine zinc	4	15	24
Globin	2	6	12
Isophane (N.P.H.)	2	6	12
Zinc suspension:			
Amorphous	½	6	10
Crystalline	2	10	20
'Lente'	½	7	20

TABLE I.—Speed and duration of action of different types of insulin preparations.

Globin and isophane (N.P.H.) insulin have an effective range intermediate between the soluble and protamine zinc varieties. The earlier hope that either of these preparations would be able to maintain control over a twenty-four-hour period has not been fulfilled and in most cases adequate therapy is only possible with two injections a day. More recently, an insulin-zinc suspension has been introduced called 'lente', which consists of a mixture of three parts of the amorphous form which has a quick action, and seven parts of the crystalline form which dissolves more slowly and produces a prolonged effect. A single injection of this insulin will produce satisfactory control in a large number of children with diabetes mellitus.

It is often observed that a few weeks after the beginning of treatment some recovery of pancreatic function may take place, enabling a reduction in insulin dosage. Infections decrease carbohydrate tolerance and during the active phase of such an illness an increase of the insulin dosage is required. If the diabetic child has to undergo a surgical operation, whenever circumstances permit he should be admitted to hospital for a few days before the procedure and the control of his diabetes maintained by using soluble insulin. The operation is most conveniently performed early in the morning and three hours beforehand the child should be given an injection of soluble insulin, followed half an hour later by a sugar drink containing 1 g. of sugar for every unit of insulin given. Three to four hours postoperatively, a further injection of soluble insulin, followed by a sugar drink, should be administered and should be repeated later. As a rule, within twelve to twenty-four hours the child can return to his ordinary diet.

The objective in the treatment of diabetes mellitus is to ensure that the child remains without symptoms and that the urine is free from acetone with no more than a trace of sugar. The blood-sugar level should remain under 250 mg. per cent. and the degree of control should enable the child to maintain normal growth and development.

DIABETIC COMA

Diabetic coma is a medical emergency precipitated by an acute deficiency of insulin. Its onset may be heralded by abdominal pain, vomiting and constipation which, when associated with guarding of the abdominal muscles, closely mimics an acute abdomen. Polyuria and thirst are rarely absent. Soon the child becomes drowsy and coma supervenes. The respirations are increased in speed and depth with the characteristic picture of air hunger, and the breath smells of acetone. Dehydration appears at an early stage with a loss of skin elasticity, sunken eyes and low ocular tension. The temperature is often subnormal and soon peripheral circulatory failure ensues. The urine will contain sugar and ketones. Albumin and some increase in the cell content are common urinary abnormalities. The blood-sugar level is raised and the alkali reserve is reduced. The blood urea is commonly elevated with a decrease in the sodium chloride content of the serum. There is usually a polymorphonuclear leucocytosis.

Treatment.—The essential needs of the child in diabetic coma are insulin, fluids and the skilled nursing required by the unconscious patient. Only soluble quick-acting insulin should be used, 20 to 30 units being injected subcutaneously as soon as the diagnosis has been established. In the presence of severe acidosis, 10 to 15 units may be given by the intravenous route. An immediate estimation of the level of the blood sugar and alkali reserve is called for and it is desirable to know the blood urea and sodium chloride content. Further blood-sugar levels should be ascertained every two hours and the initial subcutaneous insulin dose repeated at this time until the level begins to fall. Insulin dosage can then be reduced and the interval between injections prolonged. With a blood-sugar level of 300 mg. per cent. or less the sugar content of the urine can be used as a guide to further insulin requirements with blood-sugar estimations at six- to twelve-hourly intervals.

The dehydration in diabetic coma soon leads to extrarenal uræmia and peripheral circulatory failure. An adequate fluid intake can only be obtained by the intravenous route and isotonic saline is most commonly used. The latter supplies an excess of chloride with a possible aggravation of the existing acidosis but the risk is negligible when there is adequate renal function. This disadvantage led to the use of a saline lactate solution in order to supply extra sodium to combat the acidosis (Nabarro *et al.*, 1952):—

Sodium chloride	5.85 g.
Sodium lactate	3.36 g.
Distilled water	to 1 litre

Glucose is best omitted from the solution initially but as soon as the blood-sugar level begins to fall the child should receive a solution containing 5 per

cent. glucose in 0.45 per cent. saline. As the ketosis declines, the child will gradually regain consciousness and oral feeding will become possible. Only fluid, and in small quantity, should be administered initially, but as the amount is increased the intravenous drip can be discontinued. Insulin will be required two or three times a day but during the two or three days before the child can accept an ordinary diet, a sugar drink containing 1 g. of glucose for every unit of insulin should be given half an hour after the insulin injection.

Gastric lavage is advisable in the initial stages of treatment but the stomach should be left empty. In recent years attention has been focused on the considerable loss of cellular potassium in diabetic acidosis. It should be stressed that in the majority of patients the recovery is rapid and a light diet is commonly started twenty-four to forty-eight hours after the child's admission. This oral intake will soon replace the potassium deficit. There is a real danger of potassium being given in excess and it should only be administered when the serum-potassium level is low and only after a good urinary flow has been established. It should be remembered that diabetic coma is commonly precipitated by an infection and a thorough search must be made for a focus of infection and, when present, the appropriate treatment undertaken.

VASCULAR DEGENERATION

The juvenile diabetic is particularly susceptible to vascular degeneration in adult life. The blood vessels of the kidney are often affected whilst retinopathy is almost constant in those who have had diabetes for more than twenty-five years. Though such changes are more common when treatment has been inadequate, good control of diabetes is no guarantee against their development and in fact renal vascular degeneration is seen more often in the milder diabetic.

THE DIABETIC MOTHER

No review of the effects of diabetes mellitus in childhood would be complete without reference to the diabetic mother. Although the introduction of insulin made it possible for the woman with diabetes to have children without undue risk to herself there remains a high incidence of abortion and stillbirths. Premature delivery is common and many babies show congenital malformations. Those children born after the full period of gestation are often above average weight and in the early neonatal period there is the additional hazard of sudden death, the cause of which is not always established even by necropsy.

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CEREBRAL PALSY

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In 1862, W. J. Little expounded the possible relationships of 'asphyxia neonatorum' or the effects of 'some lingering labours' to the later development of brain disorder:

> 'The fœtus during the uterine contractions, especially after evacuation of liquor amnii, is subjected, together with the placenta, to a gradually increasing amount of pressure . . . the normal impediment to placental interchange reaches its maximum at the time of birth . . . should any departure from the normal act of birth take place . . . we can direct our thoughts to the necessary consequences of blood stagnation in the brain and the inevitable and mischievous cycle of affairs if this is not relieved by suitable respiration'.

Gowers (1888) was strongly of the opinion that 'birth palsies' were not uncommon. Apparently the first appearance of the term we now use came from Osler who, in 1889, wrote on 'The Cerebral Palsies of Childhood', including 120 cases of hemiplegia.

THE ETIOLOGICAL PROBLEM

The dependence of the development of the central nervous system upon normal pre-natal life, which includes an absence of genetic failure and the presence of maternal health, is appreciated. Antenatal care is all-important —the real beginnings of some of the cerebral palsy syndromes are almost certainly embryonic, and, in some, are to be found in factors in pre-natal environment. As regards birth, one of the most difficult matters to decide sometimes is whether all the events proceeding with the fœtus in its journey through the 'valley of the shadow of birth' have, in fact, been as safe as the alleged normal delivery would suppose. Suspicions of this were noted by the famous obstetrician, William Smellie, two hundred years ago when he wrote:

> 'The child being delivered, if the air does not immediately rush into the lungs, and the circulation continue between it and the placenta, the operation of tying the cord must be delayed: or, if the circulation is languid, respiration begins with difficulty and proceeds with long intervals and sometimes a great many minutes are elapsed before it begins to breathe; whatever augments the circulating force, promotes respiration, and as this increases, the circulation grows stronger, so that they mutually assist each other'.

All good practitioners now realize that the period of birth is an epoch of existence so different from those that follow it that any untoward influences during birth may well have unique effects, especially upon the nervous system at that time, but only reveal the full consequences later. The thought that some of the severe clinical cerebral palsies which ultimately emerge in a child could be due to such matters as 'cerebral anoxia' and 'birth injury', however, was only slowly accepted by the profession.

We are still very much in the dark concerning many of the causative

factors of the various disabling influences in cerebral palsy: the intelligence, the motor power, the sensory reception and perception, learning and action difficulties, and the relationship to any true associated mental retardation. Some of these factors may be more evident in the cerebral palsies of likely pre-natal origin; severe retardation and mental incapacity may weight in favour of genetic causes, although there is little clinical doubt that severe anoxia of natal origin may set up a similar picture. The balanced and careful judgments of W. J. Little deserve mention. After surveying some 200 cases of 'spastic rigidity (after abnormal labours)' and after describing their symptoms of spasms in the limbs, he boldly stated that the intellectual functions were sometimes apparently unimpaired and that in later life the individual might acquire a fair knowledge of music, the memory prove to be good and that a fair capacity for arithmetic and languages could evolve and that, in any case, many had been 'restored to considerable activity and enjoyment of life, an amelioration surprising to those who have watched'. No doubt, then, as now, good parental care and helpful guidance in a happy family aided recuperation and an improved maturation in the child who had sustained brain injury.

The more recent upsurge of interest in all aspects of the life of the child with cerebral palsy has brought with it increasing complexity of facts and opinions. We try to simplify—perhaps often oversimplify—our concepts of function and dysfunction in the nervous system. It cannot, in the nature of things, be really simple. With such a conglomerate structure as the human brain, composed of many millions of neurons and set in a chemical medium of complex metabolic pattern, undergoing, normally, in early life, rapid expansion in size and maturation and compounding sensory and motor functions with memory, emotion and initial learning—how can we comprehend the ways in which nature does try in cerebral palsy to bring about improvement in the brain-injured child? By studying the normal infant from birth onwards we are understanding more about motor action and psychomotor learning. Knowledge concerning the neural representation of movements, rather than the simpler action of a single muscle, is increasing. An increasing ability in movements indicates a progressive cerebrospinal integration and all this is significantly related to normal sensory inflow, and especially to the proprioceptive inflow from the deep and superficial parts. Sensory in-put and motor feed-back mechanisms balance up to give a normal effect of movement with coordination and so allow the natural reciprocal responses in the various muscle groups. The sensory feed-back from muscles, tendons and joints may be regarded as a 'cunningly devised' complex mechanism: partly through this, man has evolved within the attainment of a wide variety of useful general movements. As the healthy infant grows, his motor learning moves from the earlier and less organized movements on to the more complex influences of the cerebral cortex.

Some of the simplest of clinical signs—such as hypertonia or hypotonia of muscles—elude us as to causes. We still have a limited conception of the

total factors causing disablement of the ability of muscles to relax or to contract properly. Spasticity, rigidity, dystonia and such-like terms convey useful ideas of a clinical nature. In fact, our clinical terminology of cerebral palsy is mainly descriptive. As satisfactory a definition as any at the present moment is 'a persisting qualitative motor disorder, usually appearing before the age of three years, due to a *non-progressive* disorder of the brain'. One

FIG. 1.—Athetoid cerebral palsy showing abnormal posture and tonic neck reflex, in a child aged 2 years, who had neonatal hæmolytic disease with jaundice. The child is also deaf.

day—and most likely as an outcome of a careful and extensive prospective research in maternal health and fœtal welfare and in the perinatal state—we shall know a great deal more about the incidence, and classifiable (and we hope preventable) causes. For the present we must become increasingly expert and careful in the clinical assessment of developmental progress in the early months and years.

We all recognize that, whilst one or other may be specially enlightened on factors in the assessment and education of children with cerebral palsy, it is the bringing together of the doctors, teachers, psychologists and therapists in conference and discussion which gradually establishes an advancing pool of knowledge and a 'know-how' in dealing with these children. The parents, too, must be brought into the picture early, so that they may have a full acquaintance with the special educational problems in their child's case. The possible parental confusion between cerebral palsy and primary mental defect should be cleared.

POSSIBLE CAUSES

Undoubtedly some forms of cerebral palsy are *pre-natal* in origin; for instance, familial spastic paraplegia and genetical inheritance are traceable in some ataxias, hypotonias, quadriplegias, and athetotic states. There is a high incidence of prematurity in all forms of the condition, but the relationships in cause or effect are often obscure. *Natal* factors have an important place, the 'abnormal labours' which have been so often commented on at various times, especially as likely causes of anoxia. A 'cerebral' newly born

baby (premature, mature or post-mature) may make a dramatic clinical recovery, but in others the intranatal and immediate postnatal intracranial disturbance may be more sinister. Venous and capillary disturbance may be accompanied by the cerebral effects of stretching, distortion or even compression collapse of some of the arterial branches to the cerebral areas, especially in the middle cerebral and posterior cerebral arterial distributions. Effects of such vascular phenomena have been demonstrated by pathological examinations of the brain in cases of proven cerebral palsy and so-called 'boundary zone' lesions. *Postnatal* causes are related to encephalitis, meningitis, head injury, post-convulsive cerebral damage, and some of the 'vascular accidents' of childhood. Neonatal hæmolytic jaundice is of considerable significance in kernicterus and in its later effect in athetoid cerebral palsy and possibly associated deafness.

FIG. 2.—Athetoid cerebral palsy in a child aged 6 years.

Statistical analysis of causes in cerebral palsy are not yet conclusive, but in some large series of cases in different parts of the United Kingdom certain important pointers have emerged. The incidence of uterine hæmorrhage during pregnancy and/or pre-eclampsia is high in hemiplegic cerebral palsy and somewhat high in athetoid and ataxic cerebral palsy; the incidence of breech deliveries is high in hemiplegias and athetoids; the incidence of neonatal asphyxia is particularly high in quadriplegias and athetoids. In all groups there is strong evidence of neonatal illness, or a 'poor condition' in the early new-born period is likely to be recorded.

CLASSIFICATION

Various classifications have been made, the simplest being upon an objective basis: spasticity; athetosis (fig. 1, 2); ataxia; tremor; rigidity (resistance to movement through an entire range). Terms such as hemiplegia, diplegia, and the like indicate the topography (fig. 3, 4). A careful assessment of all the neuromuscular, sensory and mental factors must be made before any formal diagnostic labelling occurs.

Early diagnosis is possible—and that often implies an observant eye on a baby's attitudes, movements, reflexes and responses, and a sensitive

appreciation of the muscle tone over intervals of time. The neurology may be complex and from case to case variable, and special difficulties are added when there is some loss of special senses, e.g. hearing or vision or positional sense. Ataxic, athetoid and mixed kinds of abnormal movement—all these add up to the various difficulties intrinsic in each particular child. The unwanted movements may add to learning difficulties. Sensory re-education is important. There is nothing more helpful to the clinician in acquiring these diagnostic skills than frequent examination of good bright bonnie babies, toddlers and young children. The pre-school age-group offers particular advantages for early treatment.

FIG. 4.—Cerebral palsy. Symmetrical spastic quadriplegia in a child aged 3 years, who was prematurely born. Note the curvature of the back—his posture is that of a 6-month-old baby.

EARLY DIAGNOSIS

The diagnosis may be suspected following a difficult birth and resuscitation. Examination of the infant or child for evidence of cerebral palsy usually requires some special clinical skill, but grosser forms of hemiparesis, rigidity or athetosis may be easily detected. Milder forms of monoparesis or hemiparesis (often showing signs in the upper limb first) may pass unsuspected until sitting or standing or walking is reached. Athetoid movements may not develop until after a year or more: this type of abnormal movement may be overlooked in the early stages. Some attention should be paid to a parent's remark that 'something seems wrong in the progress'; the movements, the stiffness, the clenching, the shaking, the tension, the spasm, the difference in appearance and position of the limbs, the delay in development, increased or diminished excitability, or delay in attaining abilities or 'milestones'.

If the practitioner suspects cerebral palsy he should refer the child to a special assessment centre, such as is held in most child health departments. The clinical team will then determine the status in regard to neurological, muscular, and special sensation, mental development and ability, and try to classify the problem. Within limits, the normal variation among healthy infants must be kept in mind. Sometimes a series of observations over some weeks or months may be necessary to settle the suspicions one way or the other. Minor motor or executive disability amounting to a relatively minor form of cerebral palsy may be only suspected or detected during the early

school years. Confusion with muscular, joint, skeletal or progressive neurological disease must be carefully avoided. Every method must be brought into use to exclude or detect other handicaps: visual, auditory, sensory, mental, convulsive disorder (local or general) and, later, speech defect; perseveration of movement, 'emotional incontinence'—any or several may be present, creating 'multiple handicap' or various degrees of 'global incapacitation' which will usually have serious effects upon general development and educability. Deafness is very important and it may be unsuspected: special audiometric tests or the simpler methods as described by Mary Sheridan (1958) must be tried in order to determine the child's ability for 'auditory communication'. The psychological aspects of the child's disabilities must be ascertained by an expert in educational psychology, and herein lies a necessity to compare the cerebral palsy child with the normal range of psychological types of children rather than compare him with other cerebral palsy children.

FIG. 3—Cerebral palsy. Left hemiplegia, with sensory impairment and considerable inability of the left upper limb, in a child aged 10 years.

GENERAL MANAGEMENT

The family doctor can be of much help in, first, knowing a good deal about the child and indicating a real interest in his welfare and, secondly, encouraging the parents to apply their spontaneity and home-care skills while, perhaps, concurrently special treatments are given at a centre. The feeling and reactions of parents must be understood. Parents or doctors, or others, must not do too much or too little to aid the child's development. Like the normal, self-help, so far as is possible, should be encouraged. Over-protection or lack of provision for movement and action and enterprise may well delay favourable progress. Over-dependence can be a disadvantage. Many of the lesser degrees of cerebral palsy are benefited by the child discovering adaptations in movements, posture, balancing, gait, or writing. He may cover up some deafness by unsuspected lip reading. Teachers must also think and work with the parents. Intelligence and educability must be left to the experts to assess. It would be in the interests of all if the family doctor could be in attendance at the over-all assessment meeting when diagnostic classification, treatment and care and education are considered.

EDUCATIONAL PROBLEMS

Education may be much easier when hearing and sight are good but, even so, learning disabilities may be discovered which may introduce intricate and baffling problems for the teacher. The child may, or will, find difficulty in discovering 'a stable and understandable perceptual world' which is, in the normal, dependent upon maturation and developmental growth. The teacher must be thoroughly aware of the kinds of difficulty in perception, which will be unique in each case. This, of course, is closely related to the difficulties in learning to understand numbers, letters and words. In others, spatial problems exist concerning shapes and patterns. Motor palsy may be quite minimal in some of these cases, but any associated sensory impairment must be detected.

> 'In seeking to help these children it is important to recognize always that there is no "cerebral palsied child" but a variety of cerebral palsied children whose learning problems, personalities, and ways of adjusting to the difficulties of their lives are unique for each child. It is only through patient observation and individual work with these children that a teacher can adequately formulate a suitable learning programme, using methods adapted to the separate and different needs of the child'. (Jessie Williams.)

Doctors, teachers and therapists should be on the alert for an unexpected aptitude or ability which might slowly or even quickly emerge in a child, and, of course, parents also have much opportunity to detect and to develop further the motor ability and perceptions. Parents are the longest-term teachers.

Various factors may interfere with the education of the child: some lowering of general intelligence, perceptional difficulties, and behaviour problems. Some have abnormal and some have possibly immature electro-encephalograms. It is important to treat perceptual difficulties at the pre-school age. This can be done in a special day or residential school. All persons having care of children with cerebral palsy should be aware of special equipment which is available for the home, the school or the treatment clinic. Special chairs, tables, adaptable apparatus of many kinds and general equipment are now in common use at most cerebral palsy schools. Parents can be advised on the use of similar equipment in the child's home. Aids to development of hand and eye cooperation can be devised. Even a very light-touching typewriter can be brought into use. Special shapes, sizes and dispositions of chairs, tables and apparatus can aid the child's standing, sitting, reading, writing, and play procedures and so improve or prevent deformity. Orthopædic care is important at all stages: in appropriate cases it should be regarded as 'one of the means to facilitate and enhance conservative treatment rather than as a measure of desperation to be used only when conservative treatment has failed'.

SOME GENERAL MEASURES

Some general measures must be considered, such as good nutrition, especi-

ally avoidance of anæmia (which may arise through feeding difficulties), and a physiological supply of vitamins. Special symptoms, such as restlessness and lack of sleep, may need barbiturates or chloral hydrate. Sleep and proper rest periods must be encouraged: muscular relaxation occurs and abnormal movements disappear during the sleep. Gastro-intestinal colics and periodic vomiting may need temporary medication. Grand mal, petit mal, psychomotor disturbances, general overactivity, tremors, and other forms of bizarre movements will call for trial use of various drugs of known possible value. Curarizing drugs, although having the ability to relax hypertonic muscles, are not safely applicable. Physical therapy has much to offer: the methods now used are based on reasonably sound principles and with patience and care results, though often slow, can be achieved. The parents can help at home by giving more scope for the child and by using some simple therapy techniques. Repetitive routine may bore the child. Even the various ways of carrying, lifting or aiding the walking need skilful and subtle variations. Supporting the child in a wide warm bath will give comfort; there is some exhilaration with a sense of achievement when the child realizes that movements may be facilitated by his partial immersion. Speech training requires an expert who is keenly interested in the special methods. All therapists must, of course, work in close cooperation with the medical-educational team and must think and work with the parents.

CONCLUSION

Every endeavour must be made in antenatal care, obstetrical practice and neonatal care to prevent any factors which might be contributory to eventual cerebral palsy. Of the postnatal causes, the care of head injuries, the early and effective treatment of tuberculous or pyogenic meningitis or brain abscess or tumour are all significant. Every doctor should be aware of some of the clinical indications of the disease and the family doctor should make full use of the consultative and diagnostic facilities which are now available in each clinical area. Through early diagnosis, care and treatment, many of the less affected children can attend ordinary school and make satisfactory progress. Others can be directed to a special educational centre at an early age and favourable progress be started while the brain is still at its greatest speed of development.

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GONORRHŒA IN THE FEMALE

A FAILURE OF CONTROL

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THE present failure to control gonorrhœa is not confined to the United Kingdom. A similar experience has been noted in Australia, Canada, Denmark, Finland, France, Hong Kong, India, Poland, Norway and Sweden to name but a few.

CLINICAL CONSIDERATIONS

It has always been agreed that the reservoir of infection of gonorrhœa has been the undiagnosed female case. The male, with his long urethra usually providing a copious discharge from a gonococcal urethritis, and to whom a genital discharge is regarded as an alarming event, usually seeks advice. The infected female, however, with a short urethra producing little discharge and accustomed to menstruation, lochial discharge following childbirth and gynæcological abnormalities is less alarmed and is slower to seek advice unless prompted to do so by an angry or pained afflicted male, or by the development of complications. The symptomatology of 100 personal cases is shown in figure 1.

The symptoms or signs of gonorrhœa in the female are well known. Although the incubation period (usually two to five days but sometimes up to two weeks) is the same as in the male, this is far less apparent in an individual case. It is not possible to state how long a woman with gonorrhœa has had her infection. Traditionally the classical urethritis with a pouting reddened urethral orifice exuding pus, the red spot at one or both Bartholin ostia and the muco-pus exuding from an eroded cervix are comparatively uncommon. More often the urethritis is only evident by the ease with which a urethral smear may be obtained with a platinum loop, and the signs of cervicitis are far less definite. Sometimes gonococci may be recovered on culture when no pus is evident in the smears (Rees, 1952).

Severe complications today are relatively rare. Bartholin's abscess and salpingitis are more often encountered from non-gonococcal causes. Metastatic complications of iritis and arthritis, always apparently less common in the female, are rare indeed. Gonococcal ophthalmia in this country is also rare in spite of a dangerous fall away from the use of prophylactic measures. What does occur is a virtually symptomless carrier state with small infectious foci persisting in Skene's tubules, Bartholin's glands, the endocervical glands, or Fallopian tubes. The rectum may likewise carry

gonococci in a mild proctitis (Nicol, 1948). This may result from peno-anal coitus (Jensen, 1953). Many persons attribute the mildness of the disease to the results of chemotherapy. Pelouze (1941) indicated in his series that many patients with gonorrhœa of the mildest severity were infected by seemingly cured sulphonamide-treated males. In recent years the carrier state in the male has received increasing attention and it is obvious that a number of infectious, seemingly cured, penicillin-treated males with gonorrhœa are at large.

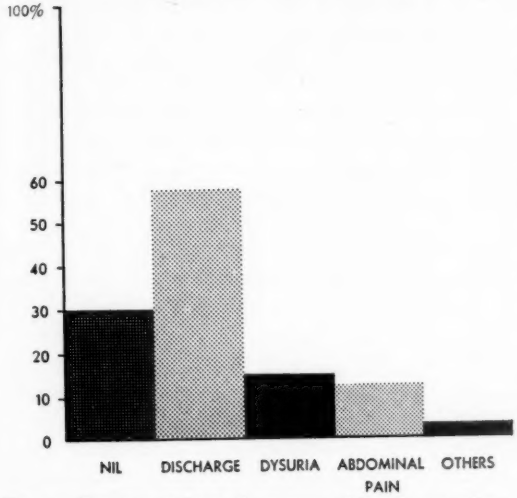

FIG. 1.—Symptomatology of 100 cases of female gonorrhœa.

In a series of 100 female cases of gonorrhœa seen at St. Mary's Hospital, in no less than 53 was the male consort known to be infected at the time of first attendance, which wholly or partly prompted the female to attend. Thirty of the patients had no symptoms at all and 19 had no obvious cervicitis or urethritis on examination. A good culture service is essential. A urethral smear alone could have diagnosed 59 cases, whilst urethral culture alone would have diagnosed 63 cases, in 24 of which the smear was negative. The gonococcus was found in the cervix in 68 instances, and in 23 of these positive cultures were obtained with negative smears. One case was diagnosed on serological grounds.

Persons with venereal disease tend to have repeated attacks. In no less than 32 of the 100 cases in this series there were 76 previous venereal incidents, and 27 had associated trichomoniasis, scabies, pediculosis pubis, syphilis, or venereal warts. Control is further impeded by heavy defaulter rates if no action is taken. In the series described, only 53 per cent. continued to attend for more than one week and 36 per cent. for more than one month.

INCREASING FAILURE RATES WITH PENICILLIN

Another reason why gonorrhœa is uncontrolled is the declining response to repository penicillins in recent years. This has occurred in spite of increasing doses of penicillin given for the disease. When penicillin was first introduced there was the fear that the dose of penicillin given for gonorrhœa might mask incubating syphilis, if present. There was therefore a tendency

to keep the dose of penicillin as low as possible. As the masking of syphilis was proved to be a bugbear (the disease usually being aborted in the incubation period or declaring itself at the usual time), the doses given were increased to make 'abortion' of syphilis more certain. In a WHO survey of 148 major V.D. clinics undertaken in 1955, in only 15.5 per cent. were doses of penicillin of 0.3 to 4 mega units given for gonorrhœa, and in no less than 84.4 per cent. doses of 0.6 mega unit, or more, were given, in 27 per cent. as much as 1.2 mega units or more.

In spite of the tendency to increase the dose, at St. Mary's Hospital, where the repository penicillin, PAM (procaine penicillin G in oil, with 2 per cent. aluminium monostearate), was once in routine use, there has been an increasing failure rate, as table I shows. The figures refer to samples of male cases which make more satisfactory material for such studies than do female cases. It will be noted that during 1956-57 the failure rates with

Year	Dose in mega units	Treated	Followed	Failures	Reinfection	Failure rate per cent.
1952	0.15	223	200	18	42	9.0
1954	0.3	226	194	9	22	4.6
1956	0.6	226	190	34	23	17.9
1957	1.2	44	39	7	15	17.9
Totals		719	623	68	102	10.9

TABLE I.—Results of treatment of gonorrhœa with PAM in London.

PAM were nearly four times what they were on a lesser dosage in 1954. When benzathine penicillin has been used, which gives dose for dose a lower peak of penicillinæmia but has a longer duration than that obtained with PAM, even worse results have been obtained (table II).

Dose in mega units	Treated	Followed	Failures	Reinfection	Failure rate per cent.
0.3	98	76	24	3	31.6
0.6	125	92	21	3	22.8
1.2	41	33	10	—	30.3
	264	201	55	6	27.4

TABLE II.—Results of treatment of gonorrhœa with benzathine penicillin in London in 1957.

Possible reasons for this deterioration might exist in the host, the environment or the organism. An analysis of our failures, where we have had increasing proportions of Negro patients, has shown the failure rates to be approximately twice as high in Negro as in white patients. In the 264 patients treated with benzathine penicillin, for example, 117 were white and there were 18 (19.1 per cent.) failures in 95 patients followed. Negro patients numbered 147 and there were 37 failures (34.8 per cent.) in 106

patients followed. The same difference between white and Negro patients has been noted not only when penicillin has been given by injection but also when given by mouth and when streptomycin has been used by injection. The Negro group, consisting mainly of West Indians in London, is by the nature of things promiscuous and it is possible that repeated reinfection resulting from a too early return to the same or similar sexual environment may partly explain the difference. Nevertheless, the failures are occurring in patients treated with repository penicillin who may still theoretically have a circulating penicillin barrier against reinfection. And the failure rate in the white group (19.1 per cent. with benzathine penicillin) contrasts with a 95 per cent. success rate with only 300,000 units when this preparation was first introduced (O'Brien and Smith, 1952). On clinical grounds therefore there is a very distinct possibility that the gonococcus has become less sensitive to penicillin. It is possible that the lessened sensitivity has become more marked in the Negro population and their mainly prostitute consorts as a result of selective breeding of less sensitive strains by repeated passage of the gonococcus and its repeated exposure to relatively low levels of penicillin as provided by long-acting penicillins.

Laboratory aspects.—There is also some laboratory evidence of the gonococci becoming less sensitive to penicillin. Some of those isolated at St. Mary's Hospital are showing lower sensitivities to penicillin than others. King (1958), at the London Hospital, has also shown that the gonococcus has a wide range of sensitivity and that some of the less sensitive strains found before treatment are sensitive only to concentrations of penicillin above that likely always to be achieved by the usual doses of repository preparations. Moreover, King and his colleagues have shown that the failures occurred predominantly in patients who initially were carrying the less sensitive strains. Whilst therefore the possibility that the gonococcus has 'acquired' some degree of resistance by developing new metabolic pathways cannot perhaps be entirely excluded until further work has been carried out, the evidence all points to the more likely possibility that the lessened sensitivity is arising from selective breeding of the less sensitive strains.

RECOMMENDATIONS FOR THE FUTURE

This poses the question of what should be given in the future for the treatment of gonorrhœa. What is required if penicillin is used is a high peak of penicillinæmia for twelve to thirty hours sufficient to overwhelm all the less sensitive gonococci. This high level should be cut off quickly so that selective breeding cannot occur in the patient as a result of reinfection immediately after treatment. The loss of the so-called 'penicillin tail', or the prolonged penicillinæmia following treatment would, however, entail two epidemiological disadvantages. This 'tail' has been considered an advantage in the prevention of reinfection during the time that the consorts are secured for treatment, and also has probably helped in reducing the reser-

voir of syphilis by curing it in the incubation period when simultaneously acquired. Indeed, repository penicillins have been used for these reasons in the routine prophylactic treatment of prostitutes in many parts of the world.

Ideally, a return should be made to aqueous crystalline penicillin, and 500,000 units every six hours for two days could be given and could probably achieve the required blood penicillin curve. After nearly fifteen years of 'single-shot' techniques, however, a return to methods involving multiple injections would be difficult to enforce. At present at St. Mary's Hospital we are using two daily injections of 600,000 units of procaine penicillin in females. It is probable that two daily injections of double this amount would be more desirable but of course more expensive.

The position with penicillin is now approximately where it was with the sulphonamides when they were first introduced into venereal diseases clinics in 1937, in so far as there was a 10 to 15 per cent. failure rate and seven to eight years were required to render them virtually useless in gonorrhœa. There is one big difference, however; 'failed' cases still usually respond to penicillin if a sufficient dose is given, whereas toxic effects prevented drastic increases in the dose during the sulphonamide era. Moreover, other drugs—e.g. streptomycin, the tetracyclines (with and without oleandomycin), erythromycin, spiramycin and chloramphenicol—are all active in gonorrhœa and can be used in the treatment of failing cases. These will prevent, or at least substantially delay, the rapid widespread dissemination of resistant strains, and penicillin therefore is still likely to enjoy a much longer innings in gonorrhœa than did the sulphonamides which became clinically ineffective against the disease at a time when there were no effective drugs available for resistant cases.

If other drugs are used, such as the orally administered antibiotics, the cost of treatment increases many times and, if widely used, a lessened sensitivity is likely to develop to these drugs also for there is already a proportion of failures occurring with their use. Streptomycin (single injections of 0.5 to 1 g.) is the cheapest alternative but the evidence points to the fact that the gonococcus might relatively soon become resistant to streptomycin. Indeed, streptomycin-resistant cases of gonorrhœa have already been reported (e.g. Davey, 1957).

SUMMARY AND CONCLUSIONS

(1) Since 1951 there has been an increase of 34.8 per cent. in the number of cases of gonorrhœa attending clinics in England and Wales, and the situation today is virtually what it was as far back as 1949. The numbers of cases seen total 68.3 per cent. of immediately pre-war times. Similar experiences are being reported in many other parts of the world.

(2) The reservoir of infection is in the undiagnosed female in whom the disease is often virtually asymptomatic and accompanied with no, or only minimal, clinical signs. Of 100 recent cases of gonorrhœa in the female,

in no less than 53 the male contact was already known to be infected at the time of first attendance. It was this fact, alone or in part, which prompted the first attendance of the female. Thirty per cent. of the patients had no symptoms at all and 19 per cent. had neither urethritis nor cervicitis on clinical examination.

(3) The desirability of a good culture service and of the performance of both smears and culture examinations on both the urethra and cervix is stressed. In these 100 cases the diagnosis could have been made by urethral smear alone in 59 patients, 39 of whom also gave a positive urethral culture. In 24 others the urethral smear was negative but the culture was positive. Urethral examination alone could thus have diagnosed 83 cases. The gonococcus was found in the cervix in 68 instances by smear or by culture including 16 of the 17 cases with negative results to urethral examination. The diagnosis was made on serological grounds alone in one case.

(4) Persons with gonorrhœa tend to acquire other venereal conditions and to have repeated attacks. In the series described, 16 per cent. had associated trichomoniasis and 11 per cent. had either scabies, pediculosis pubis, syphilis or vulvar warts. No less than 32 per cent. had had 76 previous venereal incidents.

(5) Response to treatment with repository penicillins is less successful today than formerly. With single doses of 1.2 mega units of procaine penicillin with aluminium monostearate and with benzathine penicillin, failure rates of 17 to 30 per cent. have been noted. It appears that the gonococcus is becoming less sensitive to penicillin and the implications of this are discussed. Complications in the male continue to be rare but abdominal pain believed to be due to tubal infection, albeit usually quickly resolved, was noted in 13 per cent. of the female patients reviewed.

(6) The situation in which there is a substantial increase in the number of cases, increasing failure rates to treatment combined with appreciable defaulter rates, and a large number of females infected virtually asymptomatically without their knowledge, is most disquieting and indicates a failure to control the disease.

This article is based on a lecture given at the Wright-Fleming Institute, St. Mary's Hospital, in May 1958.

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ORAL PHENOXYMETHYLPENICILLIN IN PYOGENIC HAND INFECTIONS

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In pyogenic hand infections the value of systemic penicillin therapy is well established (Gordon, 1951). The recognition of the acid stability of phenoxymethylpenicillin (Brandl, Giovannini and Margreiter, 1953) led to its clinical use with satisfactory results in many conditions including staphylococcal sepsis (Burn *et al.*, 1957). The present trial was undertaken to evaluate oral phenoxymethylpenicillin in pyogenic hand infections and to note its side-effects.

SCOPE OF INVESTIGATION

Methods.—All pyogenic hand infections previously untreated and in patients who could attend daily were accepted for the trial. The methods used were suitable for the management of these infections in general practice. In paronychiæ and in pulp infections the use of oral phenoxymethylpenicillin (penicillin V) was contrasted with parenteral benzylpenicillin (penicillin G) in an initial dose of 100,000 units together with 900,000 units of the procaine salt, followed by 450,000 units of the procaine salt daily.

Natural variation in virulence of infecting organisms and in host defences makes clinical standardization impossible and any attempt to counter the effect of variation by imposing uniformity of treatment creates artificial conditions. Each patient therefore requires individual treatment. The same criteria were used to judge the nature and timing of surgical and other treatment, and subsequent analysis showed no difference in the treatment in the separate groups. Routine bacteriological swabs were taken and penicillin-resistant cases which were not responding clinically to penicillin were treated with broad-spectrum antibiotics as soon as the sensitivity report was available. All cases in a miscellaneous group were treated with oral phenoxymethylpenicillin and were divided into those with and without lymphangitis or lymphadenitis. Cases which resolved spontaneously without forming pus were considered cured when inflammation and tenderness to firm pressure were absent. The day on which the wound first became dry was taken as that of cure in cases which discharged or were opened.

In surgical treatment the guiding principle was that of delayed minimal intervention. The operation of choice was indicated by the clinical condition: (1) saucerization if pus pointed subcutaneously; (2) incision through adjacent skin if pus in deep tissues was clearly demonstrable and definitely localized; (3) wedge resection of the nail if a subungual collection of pus was localized anteriorly; (4) avulsion of the nail if subungual pus separated the nail from the nail bed. Ethyl chloride spray provided adequate anæsthesia

for incision and nail avulsion since living tissue was not extensively involved. In all cases saucerization and wedge resection were performed painlessly without anæsthesia. In only one patient who specially requested it for nail avulsion was general anæsthesia used.

RESULTS

In paronychiæ (table I) and pulp infections (table II) oral phenoxymethylpenicillin and parenteral benzylpenicillin were apparently equally effective.

Sensitivity of organism to penicillin	Antibiotic treatment	Number of cases	Number of days to cure	
			Range	Average
Sensitive	Parenteral benzylpenicillin	10	3–7	3.8
Sensitive	Oral phenoxymethylpenicillin	12	3–8	4.8
Resistant	Penicillin and, if required, wide-spectrum antibiotics	5	5–10	7.8

TABLE I.—Comparison of results with parenteral benzylpenicillin and oral phenoxymethylpenicillin in paronychiæ.

Sensitivity of organism to penicillin	Antibiotic treatment	Number of cases	Number of days to cure	
			Range	Average
Sensitive	Parenteral benzylpenicillin	11	4–10	6.7
Sensitive	Oral phenoxymethylpenicillin	14	3–17	7.3
Resistant	Penicillin and, if required, wide-spectrum antibiotics	6	5–20	11.0

TABLE II.—Comparison of results with parenteral benzylpenicillin and oral phenoxymethylpenicillin in pulp infections.

Type of infection	Number of cases	Number of days to cure	
		Range	Average
Septic laceration	3	3–9	5.7
Palm infection	3	4–7	5.3
Pulp infection over middle or proximal phalanx	16	3–12	6.5
Total	22	3–12	6.2

TABLE III.—Miscellaneous uncomplicated pyogenic hand infections treated with oral phenoxymethylpenicillin.

In each group penicillin-resistant cases took longer to heal and this would have been still longer but for the use of wide-spectrum antibiotics. Satisfactory results were obtained with phenoxymethylpenicillin in miscellaneous infections whether uncomplicated (table III) or complicated (table IV). In all complicated cases lymphangitis or lymphadenitis was controlled within

two days. Three cases demonstrated the undoubted efficacy of oral phenoxymethylpenicillin.

Case 1.—Male aged 26, with a web-space infection. This patient reported with a four-day-old blister of his palm, having had throbbing pain for one day. Inflammation was spreading into the palm and fingers from the base of the middle finger where tenderness was maximal. Hyperextension of the middle finger was painful and axillary adenitis was present. The patient was treated with 60 mg. of oral phenoxymethylpenicillin every two hours during the day and 120 mg. at 02.00 hours during the first night. The pain lessened overnight and cure without pus formation was achieved by the seventh day.

Case 2.—Male aged 59, with early tendon sheath infection. This patient presented with an acutely inflamed, considerably swollen, forefinger, having had throbbing pain for three days. Attempted flexion was painful, and tenderness, which was present along the whole length of the flexor sheath, was exquisite in the region of the distal interphalangeal joint. After one day's treatment with oral phenoxymethylpenicillin, 240 mg. every four hours, the patient could flex his finger slightly without pain and in five days complete resolution had taken place without pus formation.

Type of infection	Number of cases	Number of days to cure	
		Range	Average
Septic laceration	2	4–5	4·5
Pulp infection over middle or proximal phalanx	2	4–5	4·5
Boil	2	6	6
Palm infection	3	6–8	7
Total	9	4–8	5·7

TABLE IV.—Miscellaneous pyogenic hand infections, complicated by lymphangitis and lymphadenitis, treated with oral penoxymethylpenicillin.

Case 3.—Female aged 42, with a collar-stud abscess. This patient attended, after four days' throbbing pain, with an acutely inflamed forefinger. Oral phenoxymethylpenicillin, 120 mg. every two hours, was given, and saucerization performed on the third day demonstrated the presence of a collar-stud abscess in the proximal anterior compartment of the finger. From the pus a pure growth of penicillin-sensitive coagulase-positive *Staphylococcus pyogenes* was obtained. Healing occurred on the fifth day.

In the miscellaneous group three unsatisfactory cases, not shown in the tables, demonstrated some of the limitations of oral phenoxymethylpenicillin. In one case penicillin was withdrawn due to diarrhœa, and two patients failed to take their tablets regularly in spite of written and careful verbal instructions.

Side-effects.—The cases described together with others in which oral phenoxymethylpenicillin was used prophylactically were reviewed for evidence of side-effects. Only patients who attended for two days after completion of the penicillin course were included. Diarrhœa (table V) was infrequent (14 per cent.) with low dosage (approximately 600 mg. a day), but was frequent (51 per cent.) with higher dosage (approximately 1,200 mg. a day or more). In 20 patients the diarrhœa was mild: not more than six

loose stools in all or more than three in any one day. In the remaining three patients diarrhœa was moderately severe and a history of dyspepsia—'gastric stomach' and 'peptic ulcer'—was elicited in two. Glossitis, sore tongue and dirty brown discoloration of the tongue were occasionally noted. Of 24 patients treated with parenteral benzylpenicillin one developed a sterile abscess at the injection site.

Bacteriological findings.—Of the 58 paronychiæ and pulp infections, 52 were opened and a swab from each grew coagulase-positive *Staphylococcus*

Approximate daily dosage of oral phenoxymethylpenicillin	Number of cases			Incidence of diarrhœa %
	Total	With diarrhœa		
		Mild	Moderate	
600 mg.	29	3	1	14
1,200 mg. or more	37	17	2	51

TABLE V.—Incidence of diarrhœa in patients receiving oral phenoxymethylpenicillin therapy.

pyogenes. In 43 cases the organism was penicillin sensitive by *in vitro* tests and in nine cases it was penicillin resistant. In two of the 43 cases a second swab was taken on account of poor clinical response and in each case penicillin-resistant coagulase-positive *Staphylococcus pyogenes* was grown. It would seem that most (83 per cent.) staphylococcal infections contracted outside hospital are still penicillin sensitive and that some cross-infection (5 per cent.) is unavoidable in spite of careful precautions in hospital.

DISCUSSION

It is clear that oral phenoxymethylpenicillin is not suitable for all patients. The patient must be relied upon to carry out instructions, and the drug is contraindicated in those liable to diarrhœa. There appeared to be an association between dyspepsia and more severe diarrhœa. The impression was strengthened when a colleague who had torrential diarrhœa—18 bright green watery stools in one day—after taking phenoxymethylpenicillin was asked about dyspepsia and replied that he had suffered from this condition for thirty years. Thus, dyspepsia appears to be a contraindication to the use of oral phenoxymethylpenicillin.

The dosage schemes found adequate were 120 mg. four-hourly (600 mg. a day, omitting the 02.00 hours dose) for moderate infections, and 240 mg. four-hourly (1,200 mg. a day) for severe infections. On account of the diarrhœa associated with higher dosage all cases were latterly treated with low doses given repeatedly to maintain therapeutic levels (approximately 600 mg. a day: 60 mg. every two hours during the day plus 120 mg. on retiring, plus 120 mg. at 02.00 hours for the first night only). On this regime, which was effective even in the most severe infections, total daily dosage was low and diarrhœa was infrequent. These practical considerations,

together with published data on blood levels which vary widely in different individuals, suggest that frequent dosage is desirable.

The advantages of oral penicillin are well known and include ease both of acceptance and of administration. Penicillin-resistant staphylococci are a problem in hospital, and in two of the present cases cross-infection apparently occurred. In general practice, however, the majority of staphylococci are still penicillin sensitive (Gould and Cruikshank, 1957) and there is little danger of cross-infection. In this series daily inspection was necessary to determine the exact day of healing but dressings need not be frequent and dry gauze is adequate.

Finally the ease of administration of oral penicillin makes it imperative to remember that the incidence of resistance to antibiotics in staphylococcal infections seems to vary directly with the extent of their use. Although penicillin was used here for paronychiæ many mild cases do well without it. Use of penicillin, however, is justifiable in pulp infections, palm infections and in the presence of lymphangitis or lymphadenitis. For these conditions oral phenoxymethylpenicillin is very suitable.

SUMMARY

In the treatment of paronychiæ and pulp infections parenteral benzylpenicillin and oral phenoxymethylpenicillin were apparently of equal efficacy.

Oral phenoxymethylpenicillin was satisfactory for most pyogenic hand infections but not all patients could be relied upon to follow directions and the drug might have to be withdrawn due to side-effects.

Diarrhœa was usually mild. It was infrequent with low dosage (approximately 600 mg. a day), but common with higher dosage. Dyspepsia, which apparently predisposed to diarrhœa, is a contraindication.

When administration of penicillin is indicated in pyogenic hand infections oral phenoxymethylpenicillin, 60 mg. every two hours during the day, is suitable. In severe infections 120 mg. should be given on retiring and at 02.00 hours during the first night of the illness.

The ease of administration is an advantage but the need for restraint in antibiotic therapy is emphasized.

It is now not only possible to treat pyogenic hand infections effectively and easily in general practice but also, because of staphylococcal infection in hospital, it is preferable to do so.

Grateful acknowledgement is made to Mr. Roland Barnes, in whose department the investigation was carried out, for advice and permission to publish cases. It is desired also to thank the casualty surgeons and nurses who assisted and some neighbouring general practitioners who knew of the investigation and referred suitable cases.

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THE CLINICAL PATTERN OF BRONCHITIS

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THE United Kingdom holds the unenviable position of having the highest mortality rate for chronic bronchitis in the world: in 1952, the mortality rate for males was 83.8 and for females 42 per 100,000 (WHO, 1953).

In order to assess the local problem in regard to the population seeking treatment, I have reviewed 469 consecutive cases of bronchitis attending the Newcastle upon Tyne chest clinic over the period 1954, 1955 and 1956.

Duration of bronchitis	Age in years							
	<10	10-19	20-29	30-39	40-49	50-59	60-69	70+
Less than 2 years	25	29	33	28	19	19	3	4
More than 2 years	1	4	27	52	68	95	56	10

TABLE I.—Age incidence of chronic bronchitis.

The usual difficulties have arisen as to the definition of the condition. I have accepted as a sufferer from bronchitis any individual who has been referred to the chest clinic with a cough and sputum, in the absence of some specific cause such as tuberculosis, bronchiectasis, lung cancer, pneumoconiosis, or heart failure due to rheumatic heart disease or hypertension. Hæmoptysis, though not of great severity, occurred in 39 (8.3 per cent.) of the cases.

AGE INCIDENCE

It would appear that the vast majority of the bronchitics have already been going for longer than two years by the time they attend the chest clinic so that irreparable damage has already been done to the bronchial tree. Long-standing bronchitis is naturally more frequent in the older age-groups. It is also clear that some individuals do not begin to suffer from bronchitis until the fourth or fifth decades. In bronchitis of longer than two years' duration, the number of cases increases progressively in the older age-groups due to the fact that it is in these groups that the symptoms become really troublesome. The decrease in the sixth decade may well represent the high mortality that occurs in chronic bronchitis in the fifth and sixth decades (table I).

SEX INCIDENCE

Ogilvie (1957) and his co-workers found the sex incidence for chronic bronchitis in subjects over thirty years of age in Newcastle upon Tyne to be 36 per cent. for males and 15 per cent. for females. Of those cases referred

by the doctors to the chest clinic, 57.5 per cent. were males and 42.5 per cent. were females. It would appear that women report sick relatively more often with bronchitis than men.

It is well known that the mortality rate from bronchitis is much higher in men than in women. This might indicate that women suffer from the condition less severely than men or that the latter, under the stimulus of being the wage earner, stay at work far longer than they should, with a consequent worsening in their bronchitis. On the other hand, children are usually referred early in their illness.

SEASONAL INCIDENCE

Although 44.5 per cent. of the patients are referred to the chest clinic during December to March inclusive, there are still an appreciable number of primary attacks or exacerbations during the remaining months of the year (fig. 1). This is due to the fact that many of the cases are already advanced and therefore suffer from attacks throughout the greater part of the year.

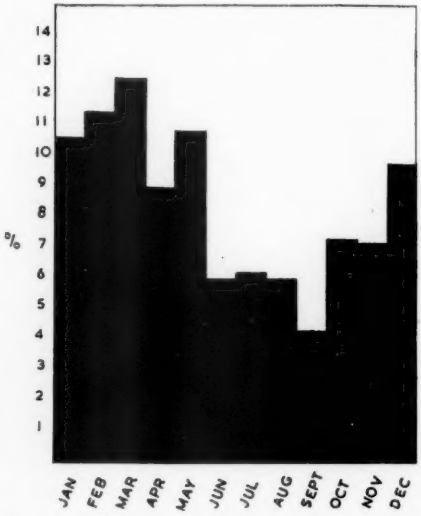

FIG. 1.—Incidence of primary attacks, or exacerbations, of chronic bronchitis.

NATURAL HISTORY

The fundamental symptom in bronchitis is excessive secretion of mucus, or bronchorrhœa, which is often purulent. At some stage in the natural history, bronchospasm is added to the symptom complex. This produces intermittent dyspnœa which merges gradually into the much more severe and permanent dyspnœa of generalized emphysema. Death finally occurs with progressive chronic pulmonary failure and hypercapnia, cor pulmonale heart failure, or with acute pulmonary failure in association with pneumonia (fig. 2).

DISCUSSION

Although we are all well aware of this general pattern, we are still very uncertain in regard to the time relationships. This is particularly true of the early stages of the disease. Considerable research work could be carried out by general practitioners into this particular aspect of the disease, as by the

time the sufferers are referred to the chest clinic or hospital, they already have chronologically advanced disease. It is also uncertain at what stage full and permanent recovery is possible. Ogilvie and Newell (1957) believe that about one-third of the cases of bronchitis recover completely. I do not

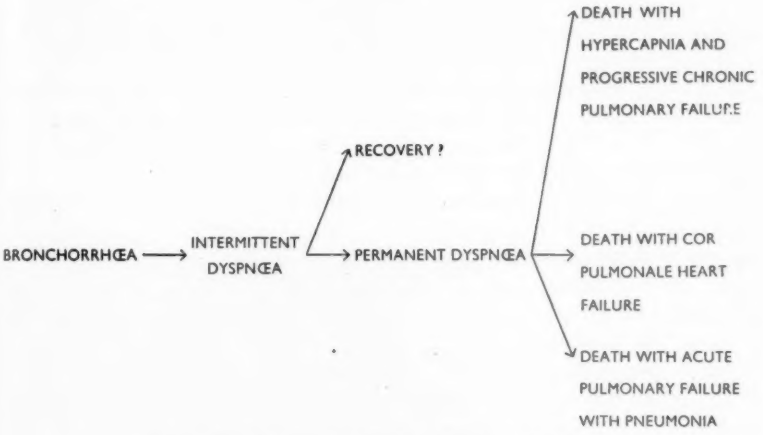
BRONCHORRHŒA
INTERMITTENT DYSPNŒA
RECOVERY ?
PERMANENT DYSPNŒA
DEATH WITH HYPERCAPNIA AND PROGRESSIVE CHRONIC PULMONARY FAILURE
DEATH WITH COR PULMONALE HEART FAILURE
DEATH WITH ACUTE PULMONARY FAILURE WITH PNEUMONIA

FIG. 2.—The natural history of chronic bronchitis.

know what percentage go on to full and permanent recovery. I certainly believe that as soon as dyspnœa is a permanent feature, recovery is not possible and we can only attempt to slow down the inevitable deterioration.

CONCLUSIONS

Many of the cases of bronchitis referred to hospital or the chest clinic are already advanced.

Although the majority of the primary attacks are delayed until the second or third decade, a not inconsiderable number occur earlier.

The sex incidence reflects the general-practitioner pattern of the disease rather than the survey pattern.

Little is known about the time relationships of the various stages of bronchitis. Full recovery is certainly not possible once the stage of permanent dyspnœa is reached.

I am indebted to Dr. C. Verity and Dr. L. Carstairs for allowing me access to some of their cases.

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A SEVENTEENTH CENTURY HEALER

VALENTINE GREATOREX, 1628-1683

By O. B. APPLEYARD, M.D.
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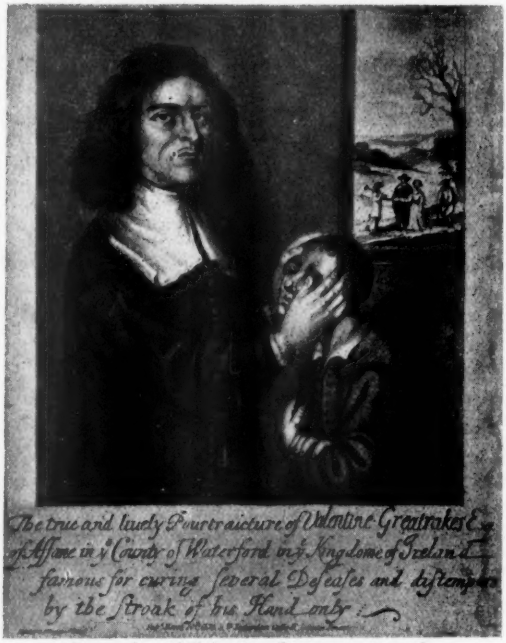
'Valentine Greatorex—a famous Irish Stroker and a Very Extraordinary Person'—'Biographica Medica,' 1799

THE ritual of healing by touch is of immense antiquity, but was particularly well known in Europe during that period of history in which the reigning members of the Royal Houses of France and England were credited with thus curing the King's Evil. It was during the seventeenth century that Valentine Greatorex, a commoner, acquired a royal if transient reputation for healing by touching or stroking. His many good qualities included kindliness, honesty and a reluctance to ask payment for his exertions, and it is to these as much as to his healing powers that he, unqualified in medicine, owed his inclusion in Benjamin Hutchinson's 'Biographica Medica' (London, 1799).


The true and lively Portraicture of Valentine Greatrakes Esq
famous for curing several Deseases and distempers
by the Stroak of his Hand only

Engraving of Valentine Greatorex at work.

EARLY DAYS

Valentine Greatorex, or Greatrakes, was born in Assane, Waterford, on St. Valentine's Day, 1628. He attended the free school at Lismore, erected by the charity of the Earl of Cork, the father of Robert Boyle who later showed much interest in his achievements. About 1640, the Greatorex family moved to England where Greatorex studied classics and divinity under Mr. Getsius, the minister of Stoke Gabriel in Devon. About 1670, Greatorex returned to Ireland and spent a year in contemplation in the castle

of Caperguin, where 'the madness and wickedness of the world' so depressed him that he declared: 'life became a burden to me'.

Possibly this frame of mind made him, in 1649, become a lieutenant in the Cromwellian Lord Roger Broghill's regiment, and he also served under the regicide, Colonel Phaire. When, in 1656, his regiment was disbanded, Greatorex turned farmer and became clerk of the peace for the County of Cork, register for transportation and justice of the peace. Here he 'took no bribes, tho' offered many', and it may have been this inconsiderate behaviour which, at the Restoration, caused him to lose his appointments. He returned to Assane, getting his living 'out of the bowels of the earth'—i.e. farming—and also helping the poor.

THE FIRST 'CURES'

It was in 1662 that Greatorex noticed 'an impulse or strange persuasion in my mind . . . that there was bestowed on me the gift of curing the King's Evil'. There were also 'voices within him, audible to noone else, encouraging him to the tryals'; to correct his unbelief, the voices 'added this Signe, that his right Hande should be dead and that the stroking of his left Arme should recover it again: the events whereof were fully verified to him . . .'.

When he told his wife she promptly decided it was all his imagination. She may have felt one 'healer' in the household was enough, because she herself had 'some small skill in surgery', and it was to her that William Mather of Salterbridge brought his ailing son. Mrs. Greatorex diagnosed scrofula, and one wonders what was her frame of mind when she referred the case to her husband, telling him that 'there was one that had the King's Evil very grievously in the eyes, cheek and throat'. Mr. Greatorex rose briskly to the challenge, for, 'I told her she should now see whether this were a bare fancy or imagination, as she thought it, or the dictates of God's spirit on my heart. Then I laid my hands on the places and prayed . . . within a month [the child] was perfectly healed'.

This result probably pleased William Mather more than Mrs. Greatorex, whose husband afterwards said that he 'cast all worldly pleasures and delights behind . . . ran the risk of catching diseases, turning my house into a Hospital and labouring day and night amidst crowds, pressings, steams and stinks of the multitudes and ulcerous persons . . . '.

As Greatorex's fame grew, so did the range of his therapy, so that in 1665 he discovered that he could cure 'the ague' which was then 'epidemical' and, despite the doubts of his wife and this time of her brother, he 'cured Colonel Phaire of Cahirmony [his former C.O.] . . . of an ague . . . and many other persons of different distempers by stroking'. He failed, however, about this time to cure Flamsteed, the astronomer, of his 'rheumatism'. Greatorex's activities were not to everyone's liking, and he was summoned before the Bishop's Court at Lismore. He invited the Court 'to his house to see the cures', for which he set apart three days a week, but there is no record of their accepting the invitation. Instead the Judge unkindly forbade him to lay hands on anyone else in future, as he had 'no Licence for prac-

tising as was demanded'. Greatorex 'disregarded the prohibition and continued to perform cures as usual', claiming that as 'he took no reward' and was only doing good to his neighbours, he needed no licence.

He seems to have won over the clerics, because in January 1666, Dean Rust of Connor and Henry More, the Cambridge platonist, were responsible for Greatorex being invited to England to treat the wife of Viscount Conway of Ragley in Worcestershire, whose headaches had defeated 'many of the ablest Physicians in England and France'. Greatorex went reluctantly. He stayed three weeks at Ragley and, although he stated frankly, 'I could not remove or abate his Ladies pain in the least . . . ', Lord Conway was very kind to him.

HIS TECHNIQUE

While in Worcestershire, Greatorex's activities so impressed 'the learned Mr. Henry Stubbe', a clergyman who also practised physic at Stratford-on-Avon, that this gentleman wrote to the Hon. Robert Boyle describing at length the stroker's appearance and technique. Mr., or as he is also styled, Dr. Stubbe, was a shrewd and impartial observer.

He noted several of Greatorex's failures, including 'giddiness, qualms of the Stomack occasioned by Hysterical vapours . . . the King's-evil', and thought that the 'Cure of one disease may be impeded by another'. Stubbe suggested that prospective patients of Greatorex might 'first advise with a discreet Physician what their Distempers are . . . the better to direct him in his Stroking'.

Stubbe described Greatorex as of 'graceful personage and presence . . . a man of very good life and of tender and charitable principles . . . modest and humble . . . ' who 'received patients with a grave and simple countenance'. Stubbe examined and smelt Greatorex's hands and detected 'no manner of Fraud', and no medicaments, 'nor was his Stroking so violent that much could be attributed to the Friction'. Greatorex 'used no manner of Charms or unlawful words . . . and always when he had done he bad them give God the Praise'. On the other hand, he quotes Lord Conway as saying that Greatorex's hand smelled 'strangely pleasant . . . [like] Sundry Flowers', whilst Dean Rust decided his urine 'smelt of violets'.

Greatorex seems always to have touched his patients, but would reject cases which were manifestly incurable. Occasionally he 'launced' tumours and wenns, but his treatment was usually non-surgical, and Dr. Stubbe watched 'the pains fly before his Hand until he drive them out at the Fingers, Mouth, toes etc. . . . and not immediately at his Touching'.

The application of Greatorex's empty glove was effective on occasion, and Robert Boyle cured a tinker by this method. Greatorex also tried rubbing with his 'Napkin and shirt . . . which I had pulled off, being very hot', but the results were disappointing. Patients were usually stripped before the rubbings, and Greatorex's spittle and urine sometimes applied, as when a boy of fourteen was cured of 'a Leprosy' by rubbing with spittle.

Evil spirits caused the healer's clientele much trouble, and he addressed one as follows:—

'Aerial Spirit, return I command thee into the Air, exercise thy natural vocation of raising Tempests and do not excite any more wind in this sad, unlucky Body'. Any sequelae, meteorological or medical, are not described, but a case of similar origin 'began to belch wind of such a vehemency that is scarce to be imagined'.

It was also evil spirits who caused some patients' 'extreme parts' to be numb to pinprick, 'but as soon as his (Greatorex's) hand should touch those parts, life and sense immediately returned . . . '. (There were always among the spectators enthusiastic clinical assistants armed with pins.)

WORCESTER INTERLUDE

From Ragley, Greatorex went to Worcester, where he was 'bruised nearly to death', and the City accounts show '£10 14*s*. for the charge of Entertainment of Mr. Greatorax'. (The only other record of reward is in Lady Conway's case, when he asked and received £150 for travel expenses and 'the hazards of the enraged seas'.) He worked hard at Worcester, 'in the Field'. Watched by Dr. Stubbe, he treated many cases of 'Falling sickness, Leprosy, Shaking palsies and the ubiquitous Evil Spirits, working amongst an infinity of diseased people until Night fall . . . '.

His most exciting case was that of Miss Welley, the schoolmistress, whom he cured of the 'Falling sickness . . . with Cryings out and Shrieks . . . excessive belchings', by stroking her 'Brest bared for this purpose'. Next day she interrupted Greatorex's dinner with a 'new Fit' so much worse than its predecessor that Greatorex thought she was 'possessed with a Devil'. Dr. Stubbe, however, had this to say: 'A Gentleman standing by Mr. Greatorex (a good while during her Fit) and saying to him "Credo quod obsessa sit", she suddenly and very brusquely replied, "Sic credo, sic credo at non Diabolo sed vento" '. This riposte, Dr. Stubbe decided uneasily, showed 'Education . . . more liberal than is ordinarily found in that Sex . . .', and Mr. Greatorex stroked her for three to four hours, 'her Pains being chaced by him out at her toes'.

LONDON CALLS

Greatorex's exertions at Worcester were terminated by Charles II who, with cheerful inconsideration, summoned him to Court one night 'by an expresse'. No details are given, but Greatorex's demonstrations before the Court at Whitehall were not a success. Nevertheless he took a house in Lincolns Inn Fields, where he healed five days a week, without 'any Follower but a Simple Youth'. His treatments were witnessed by many responsible persons, including Robert Boyle and J. A. Fairclough, M.D. Dr. Benjamin Whichcote, D.D., whom Greatorex cured of a 'very dangerous and painful malady . . . by his often application of his hand and spittle', described him as 'a sober and well-concerned person, affable, civil and courteous . . .', and the Rector of St. Paul's noted approvingly that Greatorex showed 'due reverence to his Spiritual Governors'.

Dr. Fairclough remembered the healer as 'courteous, debonair, of singular patience and tenderheartedness towards . . . pain or trouble', and praised his willingness to attempt cures although very weary after a long day's work. He approved Greatorex's preference for treating 'Seamen and Soldiers . . . to others of much higher mark and quality . . . ' and his honesty in openly stating if he felt he could not help a patient. This seems not often to have

happened and the witnesses saw 'cures . . . by strokings . . . of Dead Palsy', headaches, King's Evil and 'Cancer of the Legg'. Many patients improved after only one touching, such as the dropsical Colonel Weldon, who in full diuretic spate 'voided a very great lump of gravel, besides several smaller parcels'. But often sufferers were seen again, and the medical witnesses' reports of relapses, particularly of the 'Falling Sickness', make their testimonies all the more convincing.

There was frequent anointing with Greatorex's spittle and urine: one dropsical dame drank six spoonfuls of urine and rubbed some on her body, and for good measure was then stroked. Thereafter she passed four to six gallons of urine and 'a great store of wind'. Similar reverberations heralded the cure of a 'Widow . . . of an exceeding Timpany' of twelve years' duration, which had cost her £60 in ineffectual treatments.

> This sufferer 'snatch'd some of his urine and drank it, some of which she also put into her ears . . . some hours after the same urine began to work in her belly and she voided near four gallons of water with a great quantity of wind . . . so that now she . . . (is) . . . perfectly cured'.

Inevitably, jealousy produced enemies for Greatorex, and matters came to a head when the Rev. David Lloyd, Reader to the Charterhouse, wrote a pamphlet 'Wonders no Miracles: or Mr. Valentine Greatrack's Gift of Healing examined' (London, 1666), in which he attacked the Irishman's morals and technique. Greatorex defended himself against 'the scandalous and false reports of lying tongues' in an autobiographical letter to Robert Boyle. This included fifty-three testimonials, from eminent Churchmen, grateful patients and Andrew Marvell the poet.

The catalogue of charges was most comprehensive, the Rev. Lloyd having thoughtfully included excessive eating and drinking, incontinence with Women (with a capital W), borrowing money from patients and excommunication. Also the 'sad effect of his stroaking and launcing a poor man's sore knee in the Charterhouse and it gangren'd' and but for Dr. Bevoir and Mr. Harrison, the physician and the surgeon to the Charterhouse, there would have been 'Life and Limbe lost'. On Greatorex's behalf, Captain John Cresett declared that as the 'poor man' had already been treated by Dr. Bevoir and Mr. Harrison and dared not remove their applications from his knee for fear of their displeasure, he had asked Greatorex 'to excuse him'—which he did.

LATTER DAYS

This last encounter may somewhat have diminished Greatorex's reputation and enthusiasm, because in May 1666 he returned to Ireland to live the life of a country gentleman on the then very adequate income of £1000 a year. Although he dealt with the physical rather than the ethical component, he would probably have agreed with Molière:

> 'Of all human follies there's none could be greater
> Than trying to render our fellow-men better'.

because he now stroked only occasionally.

He re-married, and died at Assane in 1683.

GENERAL PRACTITIONERS' FORUM

RINGWORM CONTRACTED FROM CATTLE: A TWO YEARS' SURVEY IN GENERAL PRACTICE

By PETER T. MAIN, M.B., Ch.B.
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Of 384 practitioners interviewed by the Ministry of Health regional medical officers in 1932 (Ashton, 1932) to try to assess the incidence of cattle ringworm in man, 88 stated that they had never seen the disease. These practitioners were chosen because their practices were thought likely to afford them opportunities of seeing the disease, and, of the 296 practitioners who had encountered cattle ringworm, 132 considered that the disease rarely came under observation. The number of cases seen ranged from two cases in twenty-five years to five cases in one year. Since Ashton's report there have been several publications dealing with this disease, but these reports have mostly come from mycologists or from hospital dermatologists, who tend to see only the severer cases.

SCOPE OF INVESTIGATION

This study was undertaken in a Sussex general practice, mainly situated in and around the village of Burwash, and covering an area of roughly 40 square miles. The practice was an entirely rural one of approximately 2000 patients who were mostly directly or indirectly engaged in agriculture, apart from some who lived in the district but travelled to London daily to work. The study extended from October 1954 to October 1956, and the diagnosis, treatment and follow-up were carried out by myself or my partner.

The diagnosis was usually made on clinical grounds when the patient first reported to the surgery, material for pathological examination, i.e. scales, crusts and hairs taken from lesions, sometimes being obtained at the same time. This material was folded in paper and sent to Dr. Jacqueline Walker, at the Mycology Reference Laboratory, The London School of Hygiene and Tropical Medicine, who had kindly agreed to examine it. No attempt was made to wait for pathological confirmation, all the patients being given treatment at their first surgery attendance. The patients were seen at weekly intervals until the lesions had cleared up.

DIAGNOSIS AND TYPE OF LESION SEEN

Cattle ringworm is not difficult to identify in an area where the disease is occurring in the cattle. The patients were often aware that they, or their relatives, were dealing with infected cattle and had made a correct diagnosis before reporting to the surgery.

The lesions seen were of three types, depending upon the length of time

they had been present and the severity of the reaction which the fungus had produced in the skin. For convenience, these will be called lesions of types I, II, or III. The earliest lesion (type I) merely consisted of small vesicles set on an erythematous base—tinea circinata. These vesicles ruptured to give a weeping area. While the area of vesiculation spread outwards the weeping area healed with the formation of scales. The well-established lesion (type II) was the typical one seen at the time the patient came for treatment. This was a papulo-squamous, annular lesion with a clearly defined margin, exhibiting vesicles or pustules—agminate folliculitis. The central area was erythematous and usually showed scaling and a tendency to central clearing, although in some instances it showed an eczematous reaction. The most advanced lesions (type III) were almost obscured by crusting and secondary infection, but careful examination usually revealed a portion where peripheral vesiculation could be seen. The fully developed lesion showed a characteristic swollen, boggy mass, the area was often studded with pustules, and broken hairs could be seen projecting from the infected follicles. This was the kerion type of lesion.

When the lesions were multiple, it was common to find examples of all three types present at the same time.

In ringworm of type III the severity of the inflammatory reaction was such that it led to the death of the fungus and the end of the disease. Since, however, scarring could be considerable, it was desirable to try to control the lesions at an earlier stage. The patients always complained of itching, and in some the irritation was considerable.

SEX AND AGE DISTRIBUTION

During this two years' study, 31 cases were diagnosed clinically as cattle ringworm: 24 were in males (17 adults and seven children) and seven in females (five adults and two children). Of the 17 male adults, five were farmers, four cattlemen, six general farmworkers and two artificial inseminators. Of the seven male children, six were children of farmworkers (two being twins) and the other had no stated farm connexion. All five of the female adults were farmworkers' wives. Of the two female children, one was a farmworker's daughter and the other had no stated farm connexion. Thus, of 31 cases diagnosed, 28 (90 per cent.) occurred in farmworkers or in members of their families.

Age distribution.—No age of patient seems to be immune from cattle ringworm. The oldest patient was a farmer of 55 years and the youngest was a male infant of 3 weeks. This infant developed nine lesions of the type III variety on the scalp at the age of 3 weeks, after his father, who was a farmworker, developed lesions on the flexor surface of the right forearm. When he was brought for treatment at the age of 10 weeks, microscopy showed the presence of fungus, but the culture failed to show the variety. The lesions responded to gentian violet paint and were well under control after a week. Fungal infection in infants of this age is rather unusual, al-

though Bereston and Robinson (1953) reported a case of tinea capitis and corporis caused by *Microsporum audouini* in an infant of 4 weeks old, and Hubener (1957) reported tinea capitis caused by *Microsporum canis* in a 30-day-old boy.

Table I shows the age distribution of the cases. These figures seem to be in broad agreement with Rook's (1956) conclusions during a study in

Age in years	0-5	6-10	11-20	21-30	31-40	41-50	51-60
No. of cases	6	1	3	8	6	4	3

TABLE I.—Age distribution of 31 cases of cattle ringworm.

the Cambridge area. He stated that the disease was frequent in childhood and had its highest incidence during the first 20 years of working life. Rook also stated that the disease was uncommon after the age of 40. In the present series, seven cases (22 per cent.) occurred after 40 years. This relatively low age-incidence has been attributed to older farmworkers having some degree of immunity, whilst Rook and Frain-Bell (1954) have suggested that the older worker may also be more careful in avoiding possible contact, or treat himself and not consult his doctor.

SEASONAL INCIDENCE

Most authorities agree that cattle ringworm is commoner during the winter, in both cattle and man. This is accounted for by the fact that during these months the cattle are herded together in byres and pens and there is closer contact between the farmworkers and their animals. From spring, the animals are out at pasture and there is a reduction in the contact between humans and cattle. Outbreaks, however, can occur in cattle during the summer months (Ford, 1956).

It must also be remembered that the fungus can survive for a considerable period in woodwork. Walker (1955) describes an outbreak in cattle, probably due to 'scratching' posts in a field which had not been grazed for two years. She also demonstrated that parasitic spores of *Trichophyton discoides* in hair can survive for fifteen months or longer at room temperature, and found that the fungus will grow on sterilized soil and cow dung in which a conidial form occurs. She concludes that infection may occur from spores which have survived in inanimate material, such as woodwork, or from conidia in soil or animal fæces. Gentles and O'Sullivan (1957), in their survey of animal and human ringworm in the West of Scotland, showed the usual seasonal increased incidence in human infection during the winter months; in addition, their figures show a surprising peak in June, which they attribute to infection during the cleaning out of byres and pens—a task commonly performed at this time.

This peak was not found in the present study, which does, however, show the usual increase in incidence during the winter months (table II).

These figures closely parallel those of other workers (Rook, 1956; Rook and Frain-Bell, 1954), although Ainsworth and Austwick (1955) did not notice a seasonal incidence in infected cattle.

INCUBATION PERIOD

This was extremely difficult to determine when the disease had developed by direct contact with cattle, because the nature of the patient's work was

Month of onset	Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
No. of cases	6	3	4	2	2	1	0	1	1	4	3	4

TABLE II.—Month of onset of human infection with cattle ringworm.

bringing him into daily contact with his animals. Even in cases developing in the family circle it was difficult to determine the incubation period with any degree of certainty, but it appeared to be about 14 to 21 days.

SITES AFFECTED

As one would expect, the forearms, wrists and hands are most commonly affected, with the lower limbs the next most common site (table III). Rook (1956), in a study of 40 cases due to *T. discoides*, found the face, neck and head affected in 20 cases—a much higher incidence than in this practice. Of the 14 cases in which the infection was present on the hand, wrist and forearm, 13 were in male adult farmworkers engaged in handling cattle, and the other was in a farmer's wife of 32 years, who took her full share in farm work. Of the six cases in which the leg was first affected, four were in boys under 11 years. One was in a farmworker of 19, a member of a family in which five male members were infected, and the remaining case was in a farmer's wife of 32 years, who developed a lesion on the right

Site affected by disease	Forearm wrist and hand	Lower limb	Face and neck	Scalp	Trunk	Upper arm	Multiple areas
No. of cases	14	6	4	2	1	1	3

TABLE III.—Distribution of cattle ringworm.

thigh about three weeks after her husband developed the disease on both forearms.

The disease is undoubtedly most common on the exposed parts of those who become infected from cattle. The high incidence of leg-infection in children tends to support the suggestion (Carlier, 1954) that these lesions may be due to climbing gates and fences against which animals have rubbed. In familial infection, lesions can appear on any site. It is worth noting that most of the patients were convinced that they had been infected by cattle,

and many of the farmworkers were treating infected animals. There is no doubt, however, that the disease can be transmitted from one member of the family to another. In these circumstances it is worth recording the patients' (or parents') opinions as to the source of infection (table IV). Ten of the patients in whom infection was probably due to a family contact were wives or children of workers who had already been infected from

Thought to be due to cattle ringworm	Family contact, but all convinced that infection had originally stemmed from cattle	Unknown	Total
19	10	2	31

TABLE IV.—Patients' opinions of source of infection of cattle ringworm.

cattle. Thus, only two out of 31 victims who reported to the surgery were in any doubt as to the source of infection. One patient attributed the presence of ringworm in the herd to the buying of straw from a farm known to have infected animals, which is interesting in view of Walker's (1955) findings, which have already been mentioned.

Of the ten cases which were probably due to contact within the family circle, one in particular is worth mentioning.

This was in a woman of 52 years, confined to her room with pulmonary tuberculosis. Her husband, a farmer, developed lesions on his forearm and within three weeks the wife had multiple type III lesions on the trunk, the largest single lesion being 6 inches x 3 inches (15 cm. x 7.5 cm.). From these lesions, *T. discoides* was cultured, and the same fungus was isolated from an infected calf on the farm. This undoubtedly proves that human-to-human infection with cattle ringworm does occur.

MYCOLOGY

Unfortunately, samples of hair and scales were not sent for culture from many of the earlier cases, although several were examined microscopically in the surgery. Later, specimens were sent for culture from random cases. Fifteen specimens were sent for culture from the 31 cases considered to be due to cattle ringworm. The results are shown in table V.

Sometimes, only one person in a family had a specimen sent for culture, although several members of the family had the disease. From a study of

T. discoides	*T. mentagrophytes*	Microscopically positive for fungus. Culture showed only *Candida albicans*	No culture grown	Total
10	1	1	3	15

TABLE V.—Mycology of 15 cases of cattle ringworm in man.

these cases, it would seem than 18 were undoubtedly due to *T. discoides* and, if specimens from all cases had been cultured, the percentage due to *T. discoides* would undoubtedly have been much higher. As it is, all that can be said is that 83 per cent. of cases which produced a culture were due to *T. discoides*. Walker (1955) stated that *T. discoides* is the commonest

cause of ringworm in cattle, and the findings in the present study show that this fungus is the commonest cause of ringworm in man contracted from cattle, certainly in the area of this study. *T. mentagrophytes* was isolated in only one case, and, although the infection was thought to be due to cattle, it was impossible to prove this. *T. mentagrophytes* is a small-spored ectothrix, which commonly produces infection in small animals such as mice, rabbits and dogs, as well as in farm animals, such as horses, cattle and sheep.

TREATMENT

No definitive treatment was decided on during the period of the study and, as two partners were involved in treating the patients, quite a wide variety of therapy was employed. The lesson learned was that almost any form of fungicidal preparation cleared up the lesions if treatment was carried on for long enough, and the lesions were covered. It was found to be worth while to take time to demonstrate the method of application of treatment to the lesions at the first visit to the surgery and to emphasize the importance of removing infected crusts, and bandaging the lesions to prevent spread of infection. It was appreciated that the disease does tend to be self-limiting and that many of the cases would have cleared up spontaneously without treatment. It was not, however, considered desirable to put this to the test in a disease which can give rise to scarring, discomfort and in some cases loss of work, with consequent economic hardship.

Treatment included zinc undecenoate ointment B.P.C. (containing 5 per cent. undecenoic acid and 20 per cent. zinc undecenoate), ammoniated mercury ointment B.P., Castellani's paint (magenta paint B.P.C.), Whitfield's ointment (benzoic acid compound ointment B.P.C.) and gentian violet paint (crystal violet paint B.N.F.). Some cases cleared on one preparation, but in many it was necessary to change from one form of therapy to another before a response was obtained. An impression was formed that for the milder lesions zinc undecenoate ointment was quite satisfactory, Castellani's paint being best for the more advanced type III lesions. Where there was much secondary infection, sulphonamides were used, but never penicillin.

Ashton (1932) found that some cases were resistant to treatment and could cause suffering for some months, especially when there was suppuration in the scalp or beard area. He stated, however, that most cases cleared up in a few days. La Touche (1955) stated that some patients may require hospitalization for several weeks at least. Rook and Frain-Bell (1954) stated that the more inflammatory forms are self-limiting within a few weeks, but that tinea circinata can persist for months if untreated. In experimental infection in calves, Sellers, Sinclair and La Touche (1956) demonstrated that healing was spontaneous over a period of four months.

In this study, 33 periods of treatment were carried out in the 31 patients diagnosed (table VI), two patients being reinfected. The longest period of treatment was 94 days in one of these two patients and he had a subsequent reinfection which lasted 62 days, so that in a period of just over ten months,

he suffered from the disease for 156 days. The shortest time under treatment was twelve days and the average period thirty-eight days. In view of the protracted course of the disease, it was important to warn the patients of this fact; many of them required constant encouragement and support.

No. of days under treatment	12-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-94
No. of cases	7	6	7	4	5	2	1	0	1

TABLE VI.—Duration of treatment in patients with cattle ringworm.

Of the 31 cases diagnosed, only four had to be referred to a dermatologist, because of severe infection which had been unresponsive to treatment: all were due to *T. discoides*.

Case I.—A farmworker of 43 years developed his first lesion on the left forefinger while dealing with infected cattle. The infection spread to the left middle finger, the left thumb, the dorsum of the left wrist and the flexor surface of the right forearm. Two months later, lesions developed on his chest and back. He failed to respond to Whitfield's ointment and Castellani's paint. By this time, he had infected four other male members of his family. The three female members of the household were not infected. The household was a most unsatisfactory one and the parents of low intelligence. This patient was under treatment for just over five months and he slowly responded after superficial x-ray therapy.

He was unable to work for several months and his case demonstrates the economic and public health problems which can be posed by cattle ringworm. His employer was unable to employ him on the farm, because the patient was now acting as a reservoir from which uninfected cattle could become infected.

Case II.—This was the 3-year-old son of Case I, and one of twins in the family. His twin brother had lesions on the face which cleared after three weeks' treatment with Whitfield's ointment. This patient, however, had a severe kerion reaction of the scalp, which required treatment in hospital for seventeen days. X-ray treatment, hot fomentations and gentian violet paint eventually controlled the disease.

Case III.—This was the woman, mentioned already, of 52 years, with pulmonary tuberculosis, infected with the fungus from her farmer husband. The severe multiple lesions on the trunk were resistant to the usual treatments. She slowly responded to superficial x-ray therapy.

Case IV.—A man of 32 years, a cattle inseminator, developed a large lesion on the angle of his right jaw. There was considerable secondary infection. After a long and stormy clinical course, the condition settled down after x-ray therapy, hot fomentations and gentian violet paint.

DISCUSSION

Cattle ringworm seems to be a relatively common skin disease; it certainly was in the area of Sussex in which this study was carried out. *T. discoides* is the commonest cause. It is a disease which seems to be on the increase —a real increase and not merely an apparent one due to better diagnosis, because diagnosis is not difficult in an area where the disease is common in cattle. Once the disease has infected man, it spreads easily within the household and can be difficult to eradicate. Many farmers seem to treat the disease lightly when it occurs in their cattle—certainly until they or their families become infected.

It is gratifying to note the increasing interest in this disease in this

country and elsewhere, and it is to be hoped that the numerous studies of fungal infection which have been published within the last few years will in due course lead to this problem being vigorously tackled by those responsible for the health of the cattle. Many writers on this subject, and in particular Blank (1953), in Canada, have stressed the importance of cooperation between the veterinary and medical professions to control this condition. It might be worth while making ringworm in cattle and man a notifiable disease in certain areas, so that the public health authorities and veterinary officers of the Ministry of Agriculture could cooperate in an attempt to eradicate it. A great deal could also be done to educate farmers in improving the sometimes unhygienic conditions in which the cattle are kept and in the importance of regular cleaning and painting or creosote-spraying of buildings. Mortimer (1955) records an experiment in which calves in a range of buildings showed an infection-incidence of 100 per cent. three years before the experiment, whilst all calves were free from the infection during the year after the spraying of the buildings with creosote.

SUMMARY

Thirty-one cases of cattle ringworm were diagnosed during a two-year period in a rural general practice. The condition was commoner in males, and 90 per cent occurred in farmworkers or their families. There was a higher incidence of infection during the winter months.

The clinical appearances are described. The exposed sites were most commonly infected, especially the hand, wrist and forearm. Cultures showed that *Trichophyton discoides* was the fungus usually responsible.

The clinical course was often prolonged and the forms of treatment are described. Human-to-human infection is common.

It is emphasized that closer cooperation is needed between the veterinary and medical professions to work out methods of controlling the disease.

I wish to thank Dr. Margaret F. Main, who assisted me during the study, Dr. D. I. McCallum for his helpful criticism, Mr. J. Wootton, M.R.C.V.S., who obtained specimens from infected cattle, Dr. Jacqueline Walker for undertaking the cultural examination of material, and Miss Irene Kirk for her secretarial help.

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ANEURYSM OF THE AORTA

By TREVOR HUGHES, L.R.C.P., L.R.C.S, L.R.F.P.S.
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THAT aneurysm of the aorta is not a rarity is borne out by the three following cases which came to light during the ordinary routine in this practice within the space of ten months.

CASE RECORDS

Case 1.—A married woman, aged 76, who was known to have had hypertension for several years, was seen on November 26, 1957, complaining of precordial pain to the left of the sternum. The pain was boring in character. The pulse was irregular, the rate being 120 a minute. The blood pressure was 200/100 mm. Hg in the right arm and 220/120 mm. Hg in the left arm. She was x-rayed at the local hospital and the chest specialist reported that the lung fields were clear, 'but there is certainly either a markedly tortuous and uncoiled aorta or an aneurysm of the ascending aorta'. Both the Kahn and Wassermann reactions were negative.

Case 2.—A male, aged 65, was seen on May 10, 1957, complaining of abdominal pain. His history was that about six months before he had developed a dull stabbing pain in the abdomen. This had recently begun to spread across the epigastrium and down the buttocks. He had had two episodes of cerebral thrombosis: one in 1940 and the other in 1946, both affecting mainly the right arm. He had a small umbilical hernia but it was not considered that this could account for his symptoms. He was therefore referred to a surgeon who considered that he probably had an aneurysm of the abdominal aorta, and on November 25, 1957, he was admitted to St. Mary's Hospital under the care of Professor C. G. Rob, to whom I am indebted for the following details.

There was no clinical or radiological evidence of cardiac enlargement or of aneurysmal dilatation of the thoracic aorta. The pulse rate was 60 a minute, and the blood pressure was 160/120 mm. Hg. The radial and femoral pulses were normal and equal. Abdominal examination revealed the presence of a small, tender para-umbilical hernia, and a pulsatile fixed tumour to the left, above and below the umbilicus. The Wassermann reaction was negative.

Operation, on December 2, revealed the presence of a moderate-sized regular abdominal aneurysm with a separate bilateral aneurysmal dilatation of the internal iliac. There was an adequate margin between the aneurysm and the renal arteries. The aortic aneurysm was dissected and freed above and clamped. The common iliacs above the iliac aneurysms were doubly ligated and divided. The external iliacs below the iliac aneurysm were ligated proximally, clamped distally and divided between the two. The main aortic aneurysm was then removed leaving only a narrow strip along the inferior vena cava. The other arteries were secured, some from outside the aneurysm and some from below. A bifurcation terylene prosthesis was inserted, reconstructing the bifurcation between the proximal aortic stump and both external iliac arteries. The left iliac anastomosis had to be resutured because of leaking of the first anastomosis. The clamps were removed and femoral pulses were palpable both sides. Cavity closure was performed and eight pints of blood were transfused. At the end of the operation the patient was in good condition.

Postoperatively all distal pulses were felt on the right side, but on the left no foot pulses could be obtained. The femoral and popliteal pulses were good.

He was discharged from hospital on January 21, 1958, and continued to make satisfactory progress. There was some persistent œdema of the ankles which responded to oral diuretics.

Case 3.—A male, aged 66, became acutely ill in October 1957 with an attack of lumbago which lasted for a month; with treatment it improved. Unfortunately it

recurred after a fortnight's relief and a diagnosis of degenerative intravertebral disc was made. The pain persisted more or less continuously until February 1958, when he was referred to an orthopædic surgeon who agreed that the only treatment that would relieve his pain would be a plaster jacket. This was accordingly applied with complete relief of his pain.

On March 3, 1958, my partner was called to see him as he had been vomiting all night and could not retain even fluids. He looked ill and had obviously lost a lot of weight. He had no pain at this time, and sedatives were prescribed. On the same evening he collapsed getting out of bed to the toilet, and the following morning his condition had obviously deteriorated and he was seriously ill. He was referred back to the orthopædic surgeon with a view to removing his plaster jacket, and excluding a perforation of the bowel. He was accordingly admitted to hospital on March 11. When he had been in hospital in February he had had some abdominal pain which convinced us that after his period in a plaster jacket it would be advisable to obtain the opinion of an abdominal surgeon about his bowel. He died on the same day.

Post-mortem examination revealed the cause of death to be 'intraperitoneal hæmorrhage due to ruptured aneurysm of the abdominal aorta'.

SUMMARY

Three cases of aneurysm of the aorta are described, which were seen in one general practice within the course of ten months.

One of them involved the thoracic aorta, and two the abdominal aorta.

The fact that three such cases were seen within such a comparatively short space of time suggests that the condition is more common than has hitherto been suspected, and that cases may be missed because practitioners are not on the look-out for them.

My thanks are due to Dr. Clifford Jones, Chest Physician, of Wrexham for seeing and confirming the diagnosis in case 1; to Mr. Ivor Lewis of the Royal Alexandra Hospital, Rhyl, for establishing the diagnosis with certainty in the second case; also to Professor Rob of St. Mary's Hospital for undertaking the surgical treatment, and for his kind permission to publish the relevant notes; and to my partner, Dr. L. J. Cawley, for his cooperation and assistance in supplying the particulars of case 3.

A CASE OF ABDOMINAL PAIN

By R. A. KEABLE-ELLIOTT, M.B., B.S.

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The following case is instructive in more than one respect.

CASE RECORD

Mr. D. was aged 71 when he called me in because he was suffering from upper abdominal pain. His previous history was significant in that fourteen years before he had developed attacks of paroxysmal tachycardia. These had failed to respond when treated with quinidine, and he had become stabilized on digoxin, which he had been taking ever since. He had a significant degree of hypertension; at the time of this consultation his blood pressure was 190/115 mm. Hg. There had been a progressive rise in his blood pressure during the last ten years.

His immediate complaint was of pain of moderate severity, affecting the upper

part of the abdomen, maximally about two inches (5 cm.) above the umbilicus. The pain did not radiate, and, although of sufficient severity to make him a little restless, was not enough to prevent his sleeping at night. He was asked directly whether food had any effect upon it, and said that he thought that it eased it a little, but he could not be sure. Palpation of the abdomen disclosed nothing abnormal, and an examination of the cardiovascular system confirmed his elevated blood pressure. There was a second-degree systolic murmur, maximal in the mitral area, but this had been present for a very considerable time. It was thought that his pain was possibly due to a mild peptic ulcer, and he was put on a roughage-free diet, with a bismuth mixture after meals. Forty-eight hours later he was again visited at his home. He had been confined to bed since the first visit, and he admitted, again on direct questioning, that the pain was a good deal easier, and that he had obtained definite relief by taking the bismuth mixture. On this particular point he was adamant.

I was called in again twenty-four hours later, because he had had some exacerbation of his pain. Again, he was not particularly shocked, and the blood pressure this time was 210/130 mm. Hg. The pain had extended a little, being maximal at the level of the diaphragm. It was by no means unbearable, and he still said that a certain amount of relief was obtained by taking the bismuth. Examination of the abdomen was once more indecisive, but on re-examining his heart it was noted that the systolic murmur had changed, increasing appreciably in volume. It was now classified as a fourth degree systolic murmur, although no thrill was present. The correct diagnosis was now suggested for the first time. The patient remained in bed, and his pain was eased by simple analgesics alone. Two tablets of 'tercin' were given every four to six hours, and he remained perfectly comfortable. Thirty-six hours later, his wife, who was in the room below, heard a thump on the ceiling, which was his signal that he wanted attention. On going upstairs, she found him hanging over the side of the bed, having vomited about three pints (1.7 litres) of blood into a bucket by the bedside. When I arrived at the house twelve minutes later he was dead.

A post-mortem examination was performed, and the heart was found to be hypertrophied. There was a moderate degree of mitral incompetence, but no gross valvular disease. There were plaques of calcified atheromatous tissue in the descending aorta, each plaque being about the size of a two-shilling piece. At the beginning of the descending arch an elevated atheromatous plaque marked the beginning of a dissecting aneurysm, which continued down to the level at which the renal arteries were given off. This aneurysm had apparently ruptured directly into the upper right bronchus. The stomach was full of blood, but there was no ulcer or gastritis present. The rest of the body was normal for a man of his age.

DISCUSSION

This case is instructive in two respects. In the first place, it was the first case of proven dissecting aneurysm which I had seen, in which the pain was so comparatively trivial. There can be little doubt that the pain of which this patient complained was, in fact, due to a progressively dissecting aneurysm. Nevertheless, contrary to what most textbooks say, he never suffered greatly, and even the comparatively mild placebo effect of the bismuth mixture was sufficient to give him relief. The second significant point was that the diagnosis in this case could confidently be made before the patient's death. The marked alteration in the systolic murmur, occurring as it did in association with upper abdominal pain, strongly suggested the rupturing of an atheromatous plaque. It has long been my practice, where possible, to record the nature of a cardiac murmur, as suggested in the classification of Levine and Harvey (1949). In this instance, it was clearly

recorded in his records that a second degree systolic murmur was present; hence, one's clinical impression that the murmur had become louder could be immediately verified. The possibility of a ruptured valve had to be considered, but the murmur in this condition is usually much louder and associated with a thrill. One would also have expected an acute attack of cardiac failure to coincide with the rupture.

Finally, it is well worth bearing in mind the possibility of a dissecting aneurysm in all cases of supposed coronary thrombosis. Now that anticoagulants are so often administered one must be absolutely confident of the diagnosis, because obviously to give them to a patient with a dissecting aneurysm is to invite disaster. As the age of the population as a whole gradually increases, arteriosclerotic changes in the main blood vessels become increasingly marked. In these circumstances, it is only to be expected that ruptured atheromatous plaques and, indeed, dissecting aneurysms, themselves, will become much more prevalent. The majority of these cases are likely to be seen in the elderly in domiciliary practice, and their accurate diagnosis is by no means easy. This particular case well illustrates how variable the pain can be, and also the value of recording accurately the nature of cardiac murmurs, so that any alteration can be noticed and interpreted accordingly.

SUMMARY

Details are given of a fatal case of dissecting aneurysm of the descending aorta.

Reference

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EPIDEMIC WINTER VOMITING

By E. J. HOPKINS, M.B., Ch.B.
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Vomiting, often of sudden onset, is the salient symptom of this condition. The illness has a rapid, self-limiting course; recovery being complete within twenty-four or forty-eight hours in the majority of cases. The condition is infectious, probably viral, but is distinct from food poisoning due to ingestion of contaminated food or drink.

ETIOLOGY AND EPIDEMIOLOGY

As indicated by its name, the condition occurs most commonly during the winter. Outbreaks have been described by several observers (Miller and

Raven, 1936; Berry, 1952; Garland, 1952; Goodall, 1954; von Harnack, 1955, 1956; Wiesner, 1956; Hopkins, 1958). In addition, numerous epidemics of gastroenteritis not due to food poisoning or dysentery, in which diarrhœa was common or even the predominating feature, have been observed. It is probable that there exists a group of enterotropic viruses, the members of which produce varying syndromes. Reiman *et al.* (1945) and Gordon *et al.* (1947), for instance, have demonstrated that a filterable organism was probably responsible for the transmission of disease in two outbreaks of gastroenteritis, but in both these epidemics diarrhœa was the predominating symptom. Although there appears to be no agreed definition of epidemic winter vomiting, it would seem reasonable to restrict the term to cases in which vomiting is the salient feature and diarrhœa is either absent or not severe. The equivalent name used by German writers is 'Epidemisches Erbrechen'. The spread of the condition is independent of food and is probably effected by droplet infection. The incubation period is usually one to four days, but can be as long as a week.

Many descriptions refer to children and young people, but this is probably because they relate to such places as schools, children's homes, hostels and barracks, where outbreaks are much more easily observed, and do not necessarily reflect a limited age distribution. In an epidemic personally encountered the sex incidence was equal.

That the condition is common is indicated by the large number of cases, about 1,300, which Watson (1955) was able to collect from a group of general-practitioner observers. Two-thirds of the doctors participating encountered cases during the period the investigation was in progress. Many cases are so mild that the patient does not consult a doctor, whilst many cases are not recognized as being epidemic winter vomiting. The patient often attends evening surgery, saying that he has suffered from vomiting and nausea since the early hours of the morning, but now feels much better and would like a note to go back to work next day. The busy doctor scribbles a note stating that the patient has had 'gastritis', a 'bilious attack' or 'stomach upset'.

CLINICAL FEATURES

The onset of the illness is often abrupt, vomiting and nausea being the main symptoms. It often starts during the night. Commonly the patient relates that he retired to bed feeling quite well, but woke suddenly during the night and vomited copiously before being able to leave bed. The following is a typical case:—

A girl of 13 woke during the night and vomited violently. She vomited twice more during the night and had nausea and epigastric discomfort. In the morning she still complained of nausea, but examination revealed only pallor and a temperature of 99°F. (37.3°C.); there was no abdominal tenderness or guarding. The patient was restricted to fluids for the rest of the day and by the next day she had returned to normal.

If this illness had been an isolated incident, it would be impossible to make an accurate diagnosis on the clinical features alone. As an epidemic was in progress in the boarding school at the time, however, a diagnosis of epidemic vomiting could confidently be made.

A sensation of heaviness in the epigastrium is common but, although abdominal discomfort may be experienced, it must be emphasized that severe abdominal pain is not a feature of this disorder. Sometimes there is slight epigastric tenderness. Other minor symptoms, such as headache, usually frontal, and occasionally dizziness occur. The temperature is sometimes slightly raised, but rarely exceeds 101°F. (38.3°C.). The patient may exhibit the extreme pallor which is often observed in vomiting children.

DIFFERENTIAL DIAGNOSIS

The most important differential diagnosis is the acute abdomen. Intestinal obstruction, pancreatitis, cholecystitis and appendicitis may resemble epidemic vomiting. As the misdiagnosis of one of these conditions may have tragic consequences, a diagnosis of epidemic winter vomiting should not be considered until the possibility of an acute abdominal emergency has been confidently excluded.

Food poisoning of various kinds represents the most difficult differential diagnosis. In the isolated case of staphylococcal enterotoxin poisoning differentiation is usually clinically impossible. In outbreaks the main distinctive feature is that in epidemic winter vomiting the patients are usually taken ill in batches, whilst in food poisoning all the victims succumb together, after a roughly constant time-interval following the ingestion of food. A careful history of foods eaten and bacteriological investigation will, of course, facilitate accurate diagnosis. In dysentery diarrhœa is usually the predominant symptom and specimens of fæces will probably reveal the causative organism.

In Ménière's syndrome, acute labyrinthitis and epidemic vertigo a careful history should eliminate any possibility of confusion. True vertigo does not occur in epidemic vomiting. Pyrexial illnesses, such as acute tonsillitis, causing vomiting in children should present no difficulty, as long as there is adequate history-taking and examination. Although many of the cases, formerly called 'gastric 'flu', were really cases of epidemic vomiting, there is no doubt that in epidemics of influenza patients are seen with predominantly gastro-intestinal symptoms. A history of other cases of influenza in the family and the presence of upper respiratory symptoms and a higher temperature are helpful distinctive features. Cyclical vomiting and migraine are distinguished by the history of previous attacks and in the case of the latter by the predominance of headache.

Malingering and hysteria may be difficult to distinguish, particularly during epidemics in boarding schools.

TREATMENT

As the condition is so benign and rapidly resolves so spontaneously, rest and a 'fluids-only' regime are the only treatment necessary in the majority of cases. However, as the patient in general practice demands his medicine, a mixture such as magnesium trisilicate and belladonna mixture B.N.F. may be given. If the condition has not settled already, the patient will probably vomit up any medicine given orally; Wiesner (1956) therefore administered intramuscular phenobarbitone to his patients.

Rarely, in severe cases dehydration may have to be corrected by infusion of fluids intravenously.

PROGNOSIS

Most authors state that this condition is never fatal, but in an epidemic of diarrhœa and vomiting described by Hargreaves (1947) there were three deaths—all three patients were aged over 75 years. Although this outbreak was identified with previous epidemics of winter vomiting disease, the presence of profuse diarrhœa throws a certain amount of doubt on this diagnosis.

SUMMARY

Epidemic winter vomiting, characterized by violent vomiting of sudden onset, which rapidly settles down, is a common condition.

The etiology, clinical features, differential diagnosis, treatment and prognosis of this condition are discussed.

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SECTION OF GENERAL PRACTICE OF THE

ROYAL SOCIETY OF MEDICINE

DISCUSSION ON IRREGULAR UTERINE HÆMORRHAGE

January 21, 1959

Mr. Aleck Bourne (*St. Mary's Hospital*).—I shall limit myself to the clinical types of puberty, metropathia, the menopause and after, and prolonged shedding at menstruation.

PUBERTY

A minority of girls suffer from irregular, excessive and prolonged bleeding at the initiation of menstruation which causes anæmia, fatigue, apathy and anxiety. It is due to a confused evolution of the pituitary-ovarian relation, whereby there is an alternating excess or deficiency of secretion of follicular œstrogen and no development of the corpus luteum. Of Sutherland's 200 cases there were pathological changes in 53 (26.5 per cent.):—

Chronic endometritis	10 cases
Hyperplasia (metropathia)	31 cases
Endometrial tuberculosis	8 cases
Endometrial atrophy	4 cases
Normal endometrium	147 cases

Treatment.—Mild cases react to rest from school and examinations, iron, high-protein feeding and milk (for its absorbable calcium). Trial may be made of stilbœstrol (1 or 2 mg. daily), or ethisterone (25 mg. by mouth) if stilbœstrol fails after a few days' treatment. If, after a short trial, there is no improvement, or bleeding is really severe with anæmia, the uterus should be curetted and the whole of the scrapings examined microscopically. This is necessary in view of the relatively high percentage of organic changes. Curettage may cure or give a lead to specific treatment.

METROPATHIA (CYSTIC GLANDULAR HYPERPLASIA)

The endometrium is thickened and often polypoid as a result of dilatation and cellular proliferation of the glands and vascular congestion of a dense stroma. The cystic glands may be large enough to be visible to the naked eye. One ovary will be found to contain a large unruptured follicular cyst, and corpora lutea are absent.

The cause is a failure in the alternating rhythm of the pituitary secretion of the follicle-stimulating and luteinizing gonadotrophins, which interferes with the corresponding development of the Graafian follicle and corpus luteum. Prolonged œstrogen therapy will produce exactly the same endo-

metrial changes. The underlying cause may often be traced to an emotional stress. The presenting symptom is hæmorrhage, which is irregular in incidence, duration and amount. It may last for weeks and occasionally be quite severe, but may cease for as long as six to eight weeks. Vaginal examination may reveal nothing definite, but sometimes an enlarged cystic ovary on one side and mild uniform enlargement of the uterus may be felt.

Diagnosis.—Malignant disease of the cervix and corpus must be excluded by the curette and microscope. Fibroids are usually easily noticed by the irregular uterine outline but the intra-uterine fibroid polypus or small submucous fibroid may be impossible to determine even by dilatation and curettage. A fibroid polypus will cause almost continuous bleeding, but not so severe as that of metropathia nor will there be long intervals without bleeding. The doubt can be settled by anterior vaginal hysterotomy which opens the internal os sufficiently for digital palpation of the uterine cavity.

Treatment.—It is important to uncover any emotional stress and, if present, to alleviate it by the help of a psychiatrist. A severe bout of hæmorrhage may be arrested in a few hours by giving large doses of stilbœstrol (5 mg.) every two hours until the bleeding stops, but this will be followed in ten days or so by more bleeding—'withdrawal hæmorrhage'. For the commoner causes of milder bleeding progesterone (10 to 20 mg.) may be given intramuscularly for five days: a small short withdrawal bleeding will probably follow in a week. Three weeks after this stops repeat the injections of progesterone, and so on for three months. The results are often disappointing. Curettage may regularize the mildest cases and will usually be successful, at least temporarily, if the endometrium is polypoid. Hysterectomy may be necessary, especially if the patient is near the menopause.

THE MENOPAUSE AND AFTER

Apart from the minor irregularities and excesses around the ages of 48 to 50, pathological hæmorrhage of many varieties is common. Every case must be fully investigated, beginning with an inquiry as to whether the patient has been taking stilbœstrol or some other œstrogen over a long period. In about one-third of all cases the cause is malignant disease of cervix or corpus. The next common cause is probably cystic hyperplasia of the endometrium (metropathia) due to irregular endocrine involution which, in its turn, induces a high and varying secretion of ovarian œstrogen. Hyperplasia is found not only during the menopause but at any time afterwards up to many years. It may be that the ovary may be reawakened into activity, but when hyperplasia is found after the age of, say, 60, the source of the œstrogen is almost certainly the adrenal. These women may have glycosuria and hirsuties. Diagnostic curettage is necessary for every patient complaining of frequent excessive or prolonged hæmorrhage at and after the menopause. All the tissue removed must be examined microscopically. If cystic hyperplasia is found after a period of amenorrhœa the only safe treatment is hysterectomy because of the frequent risk and con-

siderable danger of either a coexisting carcinoma of the endometrium or its later development from the actively proliferating cells of the cystic glands. Common causes of blood staining apart from growths are senile septic vaginitis and cervical mucous polypi. These may be innocent but quite often at this time of life may contain a microscopic malignant focus.

A rare case of irregular bleeding which may arise at any time up to extreme old age is a feminizing ovarian tumour which secretes œstrogen. As after prolonged stilbœstrol therapy, cystic hyperplasia is inevitable and becomes malignant in as many as 20 to 30 per cent. of the cases.

If hyperplasia is found at the menopause, methyltestosterone (10 mg. daily) may be tried for not more than two months, after which a second exploratory curette should be done to discover the effect of the hormone.

PROLONGED SHEDDING OF THE MENSTRUATING ENDOMETRIUM

Normally the upper half to two-thirds of the endometrium is shed during the first three days of the period, after which regeneration begins under the influence of the rising secretion of œstrogen. If regeneration fails as a result of inadequate secretion of œstrogen the free surface of the endometrium remains ragged and bleeding. The period therefore will continue until the level of œstrogen rises to its normal physiological level. There will be bleeding for a few days or several weeks in the form of a continuous mild oozing which no drugs will stop. Diagnosis can only be made by curetting the uterus during the bleeding episode. Sections will clearly show the unhealed surface of the endometrium.

Treatment.—Stilbœstrol (1 to 3 mg.) or œstradiol (0.1 mg.) daily for a few days will stimulate regeneration and arrest the bleeding. Rather large doses are necessary to overcome the continued secretion of progesterone by a persistent corpus luteum.

Dr. E. D. Forster (*Matlock*).—The special aspects of this matter fall wholly within the province of the consultant. The general practitioner has so wide a field that he would never presume to compete with the specialist on his home ground. Nevertheless, the problems raised under the heading of irregular uterine bleeding are inescapable in general practice. In so far as he is a successful family doctor, so much the more will gynæcological problems be laid before the general practitioner for consideration and advice, and so far as he is able to contribute to a solution, so will he succeed as a family doctor. For gynæcology and obstetrics in general practice are subjects whose scientific aspect is often far outweighed by their emotional and human associations; they comprise matters which concern far more than the womenfolk, and which may affect the whole of family life. Problems of marital relations, of contraception, of therapeutic sterilization and abortion are of vital importance to the patient and to her family background. As for the doctor, at any moment they may plunge him into legal, ethical, philosophical and religious deep water, and often hot water at that! This is not to say that the scientific aspect is unimportant—matters

of life and death may be involved. One of the great difficulties in gynæcology is that certain fairly simple sign-symptom patterns may either connote real trouble, or else have a trivial basis. The sorting of these cases is his responsibility, and it may be a heavy and difficult load to carry.

The family doctor has certain advantages over the consultant, in that he knows not only the patient, but much of her past history and family background as well. But this familiarity is a two-edged weapon, and sometimes in the discovery and elucidation of serious disease it can be a real handicap. The consultant receives each case as a special problem in his own special field, and he follows in a logical order the classical procedures of history-taking, examination and special investigation. He begins at the beginning, and goes on until it is permissible to stop. But in general practice things have a way of happening upside down. Patients visit the family doctor for a hundred different reasons—they may indeed be seeking alleviation from a genuine physical distress, and in most cases this will have a straightforward, commonplace or even trivial basis. But always there exists the possibility of an undetected 'killer'. Subject to human frailty, nagged by simultaneous calls on his attention, menaced by the moving fingers on his wrist strap, the general practitioner must always be on his guard, and it is when his mind is most distracted or fatigued that the danger of a lapse is greatest.

I believe these considerations to have a general application in all general practice, but they have a particular validity in gynæcology, and perhaps a more special value in the matter of uterine bleeding.

IRREGULAR UTERINE BLEEDING

Many factors conspire to obscure the problem. How common is some irregularity of bleeding from an organ whose physiological function is to bleed, and how often an extension of this irregularity is accepted by the patient as a matter of course. What delicate ground it sometimes seems to the young girl, to the nervous and harassed housewife, to the modest spinster. What obfuscation can language interpose. The general adoption of the word 'period' to describe the monthly flow has much to answer for. The patient may well describe any uterine loss, whether the physiological flow of the menarche, the disabling drain of a threatened abortion, or an ectopic, or a hæmorrhage ten years after the climacteric, as a 'period', a 'delayed period' or a 'return of the periods'. Women have also a marked tendency to ascribe periodicity where none exists, and further confusion can occur in the timing of the menses; many patients give the interval between losses, instead of basing their calculations upon the full cycle.

The family doctor must maintain his own disciplines, and keep his own look-out; but he can be greatly helped by his consultant colleagues, not only by their receiving from him those patients who require their special skills, but by their offering him counsel for his dilemmas, and understanding for his difficulties and mistakes.

CURRENT THERAPEUTICS

CXXXV.—PEMPIDINE AND OTHER DRUGS IN THE TREATMENT OF HIGH BLOOD PRESSURE

By M. D. MILNE, M.D., F.R.C.P.

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THE recent introduction of another important anti-hypertensive drug, 1:2:2:6:6 pentamethylpiperidine (approved name, pempidine; proprietary names, 'perolysen', 'tenormal'), makes this an appropriate time to review the present status of drug treatment of high blood pressure.

Effective anti-hypertensive drugs may be classified as follows:—

(1) Veratrum and its derivatives (Kauntze, 1953).
(2) Hydrallazine (Schroeder, 1954).
(3) Ganglion-blocking drugs:
    (a) Quaternary ammonium type: e.g. hexamethonium (Turner, 1951), pentolinium, and chlorisondamine;
    (b) Amine type: e.g. mecamylamine (Allanby, 1958) and pempidine.
(4) Rauwolfia and its derivatives, including reserpine (Wilkins, 1954).
(5) Chlorothiazide (Bayliss, 1958).

The references refer to previous accounts of each drug in the 'Current Therapeutics' series.

GENERAL REVIEW

Veratrum and its derivatives are now less widely used than in 1953. Their main disadvantage is the frequent occurrence of severe nausea and vomiting. Since there is little margin between a toxic dose and an effective anti-hypertensive dose, prolonged therapy is virtually impossible.

Hydrallazine is also a potentially toxic drug, and effective doses often cause headache, palpitations, and tachycardia. In some patients the drug has caused a syndrome resembling disseminated lupus erythematosus, but fortunately recovery usually occurs on withdrawal of the drug. Most hypertensives tolerate hydrallazine less well than ganglion-blocking drugs. Hydrallazine, however, has two advantages which may make it useful when ganglion-blocking drugs are undesirable or fail to control the hypertension: (1) It is destroyed by metabolic processes and very little is excreted in the urine. It is therefore useful in cases of hypertension associated with severe uræmia. (2) It increases renal blood flow, whereas ganglion-blocking drugs reduce it. Ganglion-blocking drugs must be used with caution in cases of hypertension associated with mild or moderate uræmia (blood urea between 40 and 100 mg. per 100 ml.). If therapy causes a further rise of blood urea, hydrallazine may often be substituted with advantage.

Rauwolfia and its derivatives and *chlorothiazide* are more useful as adjuvants to the ganglion-blocking drugs than as anti-hypertensive agents in their own right. Addition of one or both of these drugs allows reduction of the effective dose of the more potent ganglion-blocking drugs, and thus diminishes the incidence and severity of undesirable side-effects. Potassium supplements, e.g. potassium chloride 2 g. thrice daily, should always be

	Quaternary ammonium type of ganglion-blocker: e.g. hexamethonium, pentolinium, or chlorisondamine	Amine type of ganglion-blocker: pempidine and mecamylamine
Absorption from the gut	Incomplete, irregular and unpredictable	Virtually complete and predictable
Excretion in the urine	Rapid and complete	Slow and may be incomplete
Renal clearance	Constant and usually equal to the inulin clearance	Variable clearance. The clearance is dependent on urinary pH, being higher in acid urine
Distribution in the body	Confined to extracellular space	Concentrated in cells and combined with cellular protein
Crossing of blood-brain barrier with possible CNS toxicity	No	Yes
Metabolism in the body	Usually not metabolized	Mecamylamine probably partially metabolized. Pempidine probably not metabolized
Evenness of ganglion-blockade	Uneven by injection Unpredictable by mouth	Steady ganglion - blockade with slow recovery on discontinuing the drug
Tolerance during initial stabilization of therapy	Tolerance prominent	Tolerance not prominent

TABLE I.—Comparison of quaternary ammonium type, and amine type, of ganglion-blocking drugs.

prescribed if chlorothiazide is used. Potassium depletion is especially undesirable in hypertensive patients as it may cause kidney damage, and hypokalæmic atony of the gut may potentiate the ileus produced by overdosage with ganglion-blocking drugs.

Ganglion-blocking drugs are undoubtedly the most potent and generally useful anti-hypertensive agents currently available, but they are far from being ideal as they often produce severe and serious side-effects. They all act by blocking synaptic transmission in autonomic ganglia, and therefore the hypotension produced is postural in type. There is little effect on the blood pressure when recumbent, but satisfactory reduction of pressure occurs in the sitting and upright posture. Apart from these general resem-

blances there are important and fundamental differences between the quaternary ammonium type of drug and the amine type, which are summarized in table I. Both types of drug have certain advantages, and it would be unwise to use one type exclusively. The practising physician should preferably familiarize himself with the use of one drug from each group. Pentolinium and pempidine are perhaps the most generally useful. There are many theoretical reasons suggesting that pempidine is a more valuable anti-hypertensive agent than mecamylamine. Pempidine, however, has not been used long enough to be certain that theory will necessarily be supported by the results of clinical practice and experience.

The most important differences between the quaternary and the amine types of ganglionic-blockers from the clinical point of view are: (1) The rapid and complete absorption from the gut of the amine type compared with the slow and incomplete absorption of the quaternaries. (2) The rapid excretion of the quaternary type compared with the slow and rather variable excretion of the amine drugs. (3) The lack of entry of the quaternary group into the central nervous system with absence of neurological complications. (4) The much greater prominence of the development of tolerance to the quaternary group during the earlier stages of therapy.

PHARMACOLOGY OF PEMPIDINE

Since pempidine is a recently introduced hypertensive agent, only four reports describing the pharmacology and clinical use of this drug have been published to date (Spinks and Young, 1958; Lee *et al.*, 1958; Harington *et al.*, 1958; Corne and Edge, 1958). The available evidence suggests that it closely resembles mecamylamine, a drug which has recently been admirably reviewed in the 'Current Therapeutics' series by Allanby (1958). There is, however, considerable experimental evidence that pempidine has several advantages as compared with mecamylamine, but it is emphasized that clinical experience with both these drugs is too short for final evaluation, and that neither compound is an ideal anti-hypertensive agent.

In a detailed comparison of these two drugs Harington and his colleagues (1958) give the following differences:—

(1) The excretion of pempidine from the body is more rapid than that of mecamylamine. A greater proportion of any dose of pempidine is directly available for excretion, because this drug enters body cells less than does mecamylamine and virtually none is bound to plasma protein. About 70 per cent. of a single dose of pempidine is excreted within twenty-four hours. If toxic symptoms from overdosage should occur, these are likely to be of shorter duration in the case of pempidine than of mecamylamine. During the initial stages of therapy, the dosage of pempidine may safely be increased more rapidly and therefore final control of the hypertension is sooner achieved.

(2) The excretion of both drugs is influenced by urinary pH, being

higher in an acid and lower in an alkaline urine. Pempidine excretion is less variable than that of mecamylamine, thus allowing more even control of the blood pressure. It is undesirable to produce a highly alkaline urine during therapy with either drug, since this increases the retention of the compound in the body with enhancement of both therapeutic and toxic effects. Soluble alkalis for treatment of dyspepsia and acetazolamide should be particularly avoided. Chlorothiazide, which is a carbonic anhydrase inhibitor, also alkalinizes the urine to some extent, but usually not enough to be clinically important.

(3) The effective anti-hypertensive dose of pempidine is usually less than that of mecamylamine when compared in the same patient. Animal experiments show that the average lethal dose of mecamylamine (Ld_{50}) is considerably less than that of pempidine. These results may not be directly applicable to human pharmacology, and longer clinical experience is necessary before the relative toxicity of the two drugs in man can be finally evaluated. The available evidence, however, suggests that the margin between an effective and a dangerous dose is greater in the case of pempidine than of mecamylamine.

The toxic effects of pempidine are similar to those of other ganglion-blocking drugs, and include constipation, dryness of the mouth, blurring of vision from paralysis of accommodation, difficulty of micturition, impotence in male patients, faintness, and syncope. Neurological symptoms including tremors, incoordination, and acute mania have been described in uræmic hypertensives treated with mecamylamine (Schneckloth *et al.*, 1956; Harington and Kincaid-Smith, 1958). Similar toxic effects have not yet been described in man from the use of pempidine. This drug, however, causes identical neurological effects in the experimental animal, and there is little doubt that similar toxic symptoms will be found to occur in the course of pempidine therapy. The desired hypotensive effect, but not the toxic side-effects, of pempidine are potentiated by simultaneous administration of reserpine, chlorothiazide, or a low-salt diet.

DOSAGE AND METHOD OF ADMINISTRATION OF PEMPIDINE

The drug is available as scored tablets containing either 5 mg. or 10 mg. of pempidine bitartrate. Treatment should be started with a dose of 2.5 mg. four times daily, best given at 7 a.m., noon, 5 p.m., and 10 p.m. Dosage should be increased daily or every alternate day by 2.5 mg. each dose, until the desired therapeutic fall of blood pressure occurs. The ideal level is a standing blood pressure of about 130/80 mm. Hg. As the rate of excretion is reduced in renal failure, a twice-daily dosage regime suffices if there is any significant rise of blood urea. If the patient complains of faintness and syncope, the doses during the day should be reduced and a double dose taken at 10 p.m. In this way efficient reduction of blood pressure may be

obtained at a time when the inconvenient effects of postural hypotension are unimportant. As in therapy with other ganglion-blocking drugs, the patient should sleep propped up with pillows or a bed-rest, in order that maximal postural hypotension occurs throughout the night. Toxic side-effects occur less commonly if adjuvants, e.g. reserpine (0.1 mg. four times daily), chlorothiazide (0.5 or 1 g. twice daily), or a low-salt diet are prescribed in addition. The last two are particularly useful if there is œdema from hypertensive cardiac failure.

Minor toxic effects may be reduced by oral neostigmine, 15 mg., or methacholine, 0.1 to 0.2 g. Constipation is an especially important toxic effect since it may progress to paralytic ileus. Patients taking pempidine should be instructed to ensure a bowel action, with aperients if necessary, preferably before the first dose of the day. If constipation occurs they should then omit one or two doses of the drug. Since excretion of pempidine is fairly rapid, a normal bowel action usually occurs and treatment can be resumed. Paralytic ileus may occur, but is usually less prolonged and severe than ileus complicating mecamylamine therapy because of the more rapid excretion of pempidine. The presence of severe neurological symptoms is an indication for immediate withdrawal of the drug. These are more liable to occur in uræmic patients, and pentolinium by injection, or occasionally hydrallazine by mouth, is a safer form of therapy.

GENERAL INDICATIONS FOR THE USE OF GANGLION-BLOCKING DRUGS

Hypertension is a condition which is extremely difficult to define. Hamilton *et al.* (1954), in fact, regard essential hypertension as the higher extreme of the normal distribution curve of human blood pressure, rather than as a definable disease entity. It is impossible to define the condition by giving limits of blood pressure sharply dividing cases of essential hypertension from the general population. Blood pressure normally rises as age advances, and readings obtained from the same patient will show some variation from day to day. Any numerical definition of an abnormally high blood pressure is therefore completely arbitrary, but there is no doubt that life expectancy is considerably reduced at higher levels of arterial blood pressure. Probably the most popular arbitrary definition is that hypertension exists if the diastolic blood pressure is constantly higher than 90 mm. Hg. The majority of individuals with a diastolic blood pressure between 90 and 110 mm. Hg are asymptomatic for many years unless they become morbidly aware of their elevated blood pressure. The current view is that these patients should be reassured and should not be treated by ganglion-blocking drugs unless complications referable to hypertensive heart disease occur. If a female patient with mild essential hypertension should become pregnant, effective anti-hypertensive therapy throughout her pregnancy will increase her chance of giving birth to a living child.

Moderate hypertension may be said to exist if the diastolic blood pressure is constantly between 110 and 130 mm. Hg. The diagnosis is usually termed 'benign essential hypertension', a complete misnomer since the course of the disease is often far from benign. The commonest cause of death is hypertensive cardiac failure and intracranial hæmorrhage. Some patients may pass into the malignant phase of hypertension, developing papillœdema with visual impairment or progressive renal failure and death from uræmia. Ganglion-blocking drugs should always be prescribed in these patients provided a form of hypertension remediable by surgery can be excluded: e.g. coarctation of the aorta, hypertension secondary to unilateral renal disease, phæochromocytoma, Cushing's syndrome, or primary aldosteronism. The patient with hypertensive cardiac failure or disabling hypertensive headaches or visual symptoms will readily appreciate the advantages of effective anti-hypertensive therapy. Management of the asymptomatic case of hypertension with a diastolic blood pressure constantly above 110 mm. Hg may be more difficult. The patient has to submit to permanent therapy which will be time-consuming and will often cause unpleasant side-effects. Oral therapy with pempidine is more likely to be acceptable than frequent injections of pentolinium. In such cases, much depends upon the personality and intelligence of the patient concerned. In selected cases, a frank discussion of the gloomy prognosis of untreated cases of moderate hypertension will convince the patient of the desirability of a treatment which undoubtedly prolongs life and delays the development of serious complications. In other patients similar frankness may lead to disabling hypochondriasis and depression, and anti-hypertensive therapy may have to be postponed until inevitable deterioration of the heart, retina, or kidneys has occurred.

The development of papillœdema or hypertensive retinitis with exudates or hæmorrhages, hypertensive cardiac failure, and proteinuria are urgent indications for anti-hypertensive therapy. Angina pectoris associated with hypertension often responds favourably to blood-pressure reduction. Cases of hypertension complicated by cerebro-vascular disease, especially recurrent cerebral thromboses, are much less suitable, and in some cases ganglion blockade may cause further deterioration. Pregnancy in a hypertensive patient is always an indication for therapy, since the risk of eclampsia is reduced and there is much more chance of the birth of a living child.

Hypertension secondary to chronic glomerulo- or pyelo-nephritis should always be treated as there is good evidence that this will delay inevitable and progressive renal deterioration (Wilson and Abrahams, 1957). Ganglion-blocking drugs provide a means of breaking the vicious circle of Bright's disease, whereby the hypertension produced originally by the primary renal disease causes further and accelerated renal impairment. The treatment of uræmic hypertensive patients, however, requires especial care. In cases in which the blood urea lies between 40 and 100 mg. per 100 ml.,

reduction of blood pressure by ganglion-blocking drugs may sometimes result in improvement of renal function. In other cases the blood urea may rise as a result of further reduction of renal blood flow. Ganglion-blocking drugs should then be discontinued and a trial made of hydrallazine which tends to increase renal blood flow. Hydrallazine may be a more suitable drug for hypertensives with severe uræmia, the blood urea being above 100 mg. per 100 ml. Here, however, the prognosis remains very grave, and patients are unlikely to respond well to any form of anti-hypertensive therapy. Some reduction of blood pressure may be of symptomatic value in protecting the retina and heart from the effects of prolonged hypertension. Hydrallazine is not significantly excreted in the urine, and therefore the dosage is the same both in uræmic patients and in those with normal renal function. In contrast, ganglion-blocking drugs are almost entirely eliminated in the urine, and the dosage in uræmia should be reduced and the drug given less frequently. Pempidine twice daily by mouth, or single daily injections of pentolinium will usually provide adequate control of pressure throughout the whole twenty-four hours.

THE CHOICE OF ANTI-HYPERTENSIVE DRUG

No final opinion can be given on the relative suitability of the quaternary or amine type of ganglion-blocking agent in any particular case. The quaternary type, e.g. pentolinium, is more rapid in action and is more useful if it is necessary to reduce the blood pressure urgently, as in cases of malignant hypertension or severe hypertensive cardiac failure. If desired, an amine type of ganglion-blocker, e.g. pempidine, may be substituted when the acute symptoms have been controlled. The chief advantage of the amine type of ganglion-blocker is free absorption from the gut making injection therapy unnecessary. These drugs are easier to use in the conditions of general practice. They exert a prolonged and even action, and it is therefore unnecessary to assess the blood-pressure reduction at any set time after administration of the drug. In contrast, in a patient treated by injections of pentolinium, the blood pressure should be measured at the time of maximum effect about 30 minutes after an injection.

Some patients, however, find the prolonged and unremitting ganglion blockade produced by pempidine or mecamylamine completely intolerable. Patients of both sexes may suffer from constipation unrelieved by aperients, and male patients may complain of impotence. The patient treated by injections of pentolinium usually learns that bodily functions requiring autonomic control are facilitated at times just before an injection when ganglion blockade is at a minimum. The most suitable drug is that which in practice adequately controls the blood pressure, and at the same time results in minimum inconvenience and toxic side-effects. The management of all patients is made easier by use of adjuvants such as reserpine or chlorothiazide. The use of the quaternary type of drug by mouth should

be reserved for the few patients who refuse injection therapy and who have been proved unsuitable for oral treatment with pempidine. The special indications for hydrallazine in selected uræmic patients have already been discussed.

PROGNOSIS

Patients with malignant hypertension who have been effectively treated before there has been deterioration of renal function show the most unequivocal improvement in prognosis (Kincaid-Smith *et al.*, 1958). Here the outlook has been almost revolutionized by use of ganglion-blocking drugs. Previously, almost all such patients died within two years of the diagnosis, but now they may often enjoy many years of comparative good health. The management of cases of hypertensive heart failure is more satisfactory since reduction of blood pressure lessens the strain on the left ventricle and often prevents further deterioration of cardiac function. Conception in a hypertensive patient is now no longer an indication for termination of pregnancy, and many healthy children may be born who would previously have inevitably perished *in utero*. The prognosis in the patient with mild and uncomplicated hypertension is good without therapy, and most physicians consider that these patients live happier and more comfortable lives without the undesirable symptoms induced by ganglion blockade.

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PRACTICAL DIETETICS

III.—LOW-RESIDUE DIETS

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WHENEVER a low-residue regime is necessary the foods taken must be of good quality, but need not be expensive. They must be fresh when purchased, freshly cooked and with as little delay as possible from the cooking-pot to the table. It is most unwise to take large amounts of food at any one meal. The foods must be easily digested and the patient is well advised to eat slowly and to chew the food well. Fluids are better taken between meals and never taken very hot. Adherence to these simple rules will prevent the feeling of fullness so many patients complain of and which is so often distressing and painful.

It is important to strain all fruit juices, and all vegetables must be sieved so as to be free of stalks, skins and pips.

Such a regime is prescribed in conditions such as acute diarrhœa following a period on a liquid diet, chronic diarrhœa, amœbic or bacillary dysentery, convalescence from typhoid fever, colitis, ulcerative colitis, Crohn's disease and certain pre- and post-operative conditions.

FOODS ALLOWED IN A LOW-RESIDUE DIET

Beverages:	Freshly made weak tea or coffee, Oxo, Bovril, Marmite Take one pint of milk daily (do not overdo the milk intake)
Breads:	Light breads and rolls (avoid coarse breads) Plain scones, shortbread
Cereals:	Fine oatmeal, cornflakes
Cakes:	Plain madeira cake, plain sponge cakes (avoid rich pastries) Plain, sweet biscuits without nuts or currants
Desserts:	Boiled egg-custards, baked egg-custards Junkets, jellies made of fresh fruit juice, milk-jellies, egg-jellies Meringues, plain sponges soaked in fruit juice Sponge puddings, bread-and-butter puddings Ice cream
Fruit:	Strained fruit juice, e.g. orange, pineapple, strained canned fruit juice to serve as sauces. Fruit purée, e.g. apples, prunes, pears. Baked apples with syrup and honey. Ripe bananas
Fats:	Butter, fortified margarine Cream salad-dressing or salad oil
Meats:	Sweetbreads, tripe, brains, liver Tender roast or grilled meat Boiled meat, e.g. mutton, lamb, ham Poultry, e.g. chicken, or small portion of duck or turkey Grilled bacon
Eggs:	Boiled, poached or whisked in milk
Fish:	Steamed, baked or grilled
Cheese:	Cheddar, Cheshire, Double Gloucester, cream cheese

Potatoes: Boiled, baked or jacket, mashed

Macaroni: Spaghetti, noodles

Rice: Well cooked

Soups: Bouillon broths, and cream strained soups

Vegetables: Strained tomato juice
Cooked and sieved green vegetables
Cooked and mashed root vegetables
(*N.B.*—The flower of cauliflower need not be sieved)

Sauces: Meat juices, simple gravies. White sauces. Vinegar, lemon juice

Sweets: Plain and milk chocolate
Boiled sweets, Turkish delight, marshmallow

FOODS TO AVOID IN A LOW-RESIDUE DIET

Bread: Coarse breads and biscuits

Cereals: Coarse oats and whole-grain cereals

Meat: Hot fat, roast pork, canned meats, sausages, tough meats

Fish: Crab, lobster and the bones of fish, canned fish

Cheese: Gorgonzola, blue-vein

Miscellaneous: Nuts, stones, seeds, currants, raisins, sultanas, sharp cores, peels or stalks, gherkins, olives, pickles, relishes, spices, ketchup
Avoid all fried foods
Chew your food well
Look forward to your food and enjoy it.

SAMPLE MENU FOR A LOW-RESIDUE DIET

Breakfast:
Half wine-glassful of fresh fruit juice
Freshly made weak tea or coffee
Milk or cream and sugar as desired
Fine cereal, syrup or milk or both
Soft boiled or poached egg
Bread toasted, about one slice
Butter as desired
Honey, syrup or jelly-marmalade

Mid-morning:
Tumblerful of milk
Horlicks or Ovaltine, and sugar as desired
One plain, sweet biscuit

Lunch:
Bowl of chicken or veal-bone broth
Small portion of tender roast beef together with the meat juice
Boiled potatoes with melted butter
One slice of bread and butter if required
Dessert: Junket or small portion of egg custard
Freshly made weak tea or coffee with milk and sugar

Tea-time:
Freshly made weak tea with slice of lemon or milk and sugar as desired
One slice of bread and butter as toast
A little jelly jam

Dinner/Supper:
Half a wine-glassful of fresh fruit juice
Slice of cold or hot boiled ham
Baked potato in jacket *or*
poached egg on mashed potatoes
One slice of bread and butter as toast
Dessert: Small portion of apple purée
Freshly made weak tea or coffee

Bedtime:
Oxo or Bovril plus a little Marmite
One plain biscuit

REVISION CORNER

MIGRAINE IN CHILDHOOD

CONTRARY to the older teaching, migraine is one of the commonest puzzles which family practitioners and school doctors refer to specialist clinics. It presents much more often, for instance, than epilepsy, congenital heart disease or mental defect.

DIAGNOSIS

As a safeguard against loose thinking, the syndrome needs to be defined. Even in childhood we commonly see the classical picture of *periodic pallid prostration with paræsthesiæ, puking, and pain.* Anorexia also is almost invariable in the attacks, and a strong family history is common. I would not reckon as migraine a story of recurrent headaches in the absence of prostration and abhorrence of food. Such paræsthesiæ as children experience are mostly visual with various patterns of sparkling lights or blacked-out areas and, in four of my older cases, hemianopia. The subjects of migraine usually have normal sight, and the ophthalmic clinic should not automatically be burdened with every case on the supposition of 'eye-strain'. Incomplete forms of the syndrome are common in children, as in adults.

It has been argued that migraine would be a misnomer for children without headache, and the term 'periodic syndrome' has therefore been proposed instead to cover those groups of children with recurring bilious attacks who used to be labelled 'acidosis' or 'cyclical vomiting'. But hemicrania is not a restrictive title which can limit the use of the name migraine according to a single one of its symptoms. In my view, to introduce a diagnosis of 'periodic syndrome' leads to a regrettable complexity, uncertainty and fragmentation of what is in fact a unitary syndrome and a very common one throughout childhood and adult life.

DIFFERENCES FROM ADULTS

Children may vary from adult experience in three important ways:—

(a) The child's description of his attacks is necessarily less convincing and recognizable in words than that of an older observer. But the sequence of physical signs is diagnostic enough, even in pre-school children, with stereotyped episodes lasting one to three days.

(b) The attack commonly appears to be feverish, and this is not merely a matter of cutaneous dilatation in the carotid distribution. The febrile onset places on us the onus of excluding relapsing urinary-tract infection by microscopy, and of disallowing mere recurring virus respiratory infections which commonly cause anorexia and headache and maybe some vomiting. It does seem, however, that infections, like menstruation, can

trigger migraine attacks. Conversely, the skull-base pain of some migraine cases can simulate sore throats and lead to unnecessary tonsillectomy.

(c) The younger the child, the more likely is it that colicky abdominal pain, rather than head pain, may attract notice. Older subjects are better able to interpret the churning discomfort of deranged visceral motility which underlies their nausea, retching and vomiting. 'Abdominal migraine' in childhood is not a different entity from migraine in adults, but the child's description tends to emphasize the abdominal components of the syndrome in a way which must not be allowed to head us off from the diagnosis of migraine, and which should set us on guard about possible misdiagnosis as a surgical emergency. In one of my patients the pain was sub-sternal and the mother failed to recognize its nature, although she had half a lifetime's experience of her husband's classical migraine.

It is easy to see how often the doctor is faced with worry about the appendix in children with migraine, especially if the patient falls sick on holiday away from home. Parents are too trustful to presume to intrude a remark, once they have heard the word 'appendicitis' pronounced. One mother respected our professional infallibility so much that she refrained from pointing out to the surgeons that it was the second day of one of her daughter's familiar classical migraine bouts when the doctor sent her into hospital. The usual laboratory report on such appendixes is 'congested'. It is not always as an acute emergency that the migrainous child is misdiagnosed as appendicitis. The doctor, after a dozen episodes of obvious illness, vomiting and abdominal pain, may be pressed by parents for radical surgical relief, so that the abdomen is eventually opened under the mythical title of 'grumbling appendix'. The rationale, however, is no better than 'try anything once'—like tonsillectomy for similar periodic episodes—and the results are commensurate with the indications.

THE REPROACH OF MIGRAINE

Delicate? The migrainous child is a puzzle and consternation to teachers, parents and practitioner and to himself. His recurring attacks are mystifying and mortifying. Parents infer that symptoms which produce such frequent prostrating upsets must necessarily be serious. And teachers will be filled with either compassion or exasperation, taking the sallow-green complexion and homegoing as in some way a reproach to the school and to school dinners. In every respect but the actual attacks, however, the health of the migraine subject is normal.

Epileptic? Parents may worry over the suggestion that migraine is a variant of epilepsy, since rarely the two coexist. The reverse explanation is probably a better one, that epileptic seizures may be induced, in subjects liable to epilepsy, by the cerebral anoxia of carotid vasoconstriction during migraine attacks.

Psychogenic? There is an unfair hint of reproach in the insinuation that migraine attacks are due to instability of the 'nerves'. My experience is that

children of widely differing temperaments and intellects are liable to migraine; and I have not found any high correlation with emotional stress, though, admittedly, there are a few children who have missed all their own birthday parties for years. Migraine is a recurring perverse vasomotor prank. To call it a stress disorder is to miss the true perspective, and is unfair to the subjects of this particular circulatory mechanism. Migraine is a somatic condition which may be precipitated or aggravated by a wide variety of causes, including sometimes psychic stress; but it is no more intrinsically psychogenic than, for example, menstrual herpes. Stress enters into it undoubtedly when the migrainous child gets spectacles prescribed unnecessarily, or loses his tonsils, or undergoes appendicectomy during an attack.

PROGNOSIS

Parents can be assured that many children who have unmistakable migraine episodes in early or middle childhood will lose their attacks entirely, or the frequency and intensity will be so much reduced after a few years as to cause negligible inconvenience. On the other hand, of course, there are patients who only begin to have trouble with migraine in later childhood, or adult life.

MANAGEMENT AND TREATMENT

Migraine is one of those conditions, like respiratory allergy, with which the patient has to come to terms without vain fretting or insistence that the doctors must abolish it outright. Morale must be upheld. The very fact of clarifying the diagnosis is an immense relief to many parents and their children, because it gives a respectable and yet benign explanation for the child's bewildering episodes, so that all the nightmare fears of brain tumour, mental aberration, meningitis, appendicitis and bowel obstruction can be ruled out. It is desirable that the school medical officer should warn teachers of the nature of migraine attacks so that they may be treated calmly and without vexation. The child's record of absence from school should be kept under review.

Children with infrequent attacks do well enough with an adequate dose of soluble aspirin at the very outset and a couple of hours' sleep in bed.

If attacks occur several times a month it will be worth trying the effect of sedation, such as phenobarbitone, $\frac{1}{2}$ grain (30 mg.) twice daily, or three times daily for a big child. There may also be value in one of the more sedative antihistamine preparations. And there are newer drugs awaiting evaluation, for continuous administration.

Whenever the patient can predict the onset, either by visual or other disturbances, the indication is to secure immediate absorption of one of the compound ergotamine preparations. The essence of this is to get the drug into the circulation within twenty minutes, so that secondary carotid vasodilatation may be prevented. Older children can take a tablet to school.

I have known a grammar-school boy's school attendance transformed by carrying 'migril', which contains ergotamine tartrate 2 mg., cyclizine hydrochloride 50 mg., and caffeine 100 mg. These preparations are not suitable for prophylactic continuous daily use.

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GLANDULAR FEVER

THE number of cases of glandular fever which are being diagnosed is on the increase—probably due to a greater awareness of the disease rather than a true increase in prevalence.

HISTORY AND ETIOLOGY

The first description of the disease was by Pfeiffer in 1889, when the enlargement of the glands together with fever was the principal feature. For the first twenty years of this century little was heard of the condition, but in 1921 Tidy and his colleagues associated the glandular enlargement with the increase of mononuclear cells in the blood and suggested the name of infectious mononucleosis. In 1932, Paul and Bunnell discovered that cases of glandular fever had a heterophile antibody in the serum to the red blood corpuscles of sheep and considered it specific for the disease. Since that date many cases which appear to be glandular fever on clinical and hæmatological grounds have been recorded in which the Paul-Bunnell test is negative. In a small series of cases, for instance, Schubert *et al.* (1954) tried to differentiate between those which gave a positive reaction and those which were negative, pointing out that in the former the lymphocytosis was in excess of fifty per cent. whilst in the latter it was less. Recently in a large field trial Hobson and others (1958) noted that one in three of the cases had negative Paul-Bunnell reactions and drew attention to age and seasonal differences associated with the two groups. In this series they were unable to confirm the differences in the lymphocyte counts.

The wide variety of symptoms and clinical findings which may be associated with glandular fever has suggested that it may in reality be more than one disease. It is generally believed to be of virus origin and more than one virus may be responsible. The involvement of glands and the hæmatological changes have suggested the possibility of a sensitization phenomenon.

The disease is usually found sporadically but outbreaks do occur in which there is a high incidence rate among those at risk. The incubation period is probably 10 to 15 days but much longer periods have been recorded.

CLINICAL FEATURES

For the sake of description it is convenient to divide the cases into three clinical groups: (1) a glandular type in which the enlargement of the glands

is the outstanding characteristic, (b) an anginose type in which the prominence is on the throat symptoms, and (c) a febrile type which presents itself as a pyrexia of unknown origin.

In many the onset is often of an upper respiratory-tract infection associated with pyrexia and a varying degree of sore throat. Hæmorrhagic lesions in the mouth, particularly petechial, are associated with the disease and Holzel (1954) described them as being often found along the line of the junction of the hard and soft palates.

Glandular type.—In the glandular type the prodromal symptoms are followed in about four or five days by enlargement of the glands, usually in the neck where both anterior and posterior groups are involved, but often in the axillæ and groins as well. The glands are small and discrete and tender to the touch. The deep glands as well as the superficial ones may be involved and, indeed, in some cases may be the only ones affected. This leads to even greater difficulties in diagnosis as the symptoms may be those of a chest infection with a troublesome cough if the mediastinal group is enlarged; alternatively the mesenteric group may cause abdominal discomfort with vomiting and diarrhœa and cases have been operated on for suspected appendicitis. In a few, mild jaundice is sometimes seen which is probably the result of a hepatitis rather than obstruction by enlarged glands as was at one time thought. In others, meningitic symptoms are found associated with a lymphocytosis in the cerebrospinal fluid. The glands may remain palpable for several weeks although the pyrexia in this type seldom lasts more than fourteen days. Recrudescences and relapses are not infrequent.

Anginose type.—When the throat condition is the prominent symptom the typical appearances are found between the seventh and the tenth day of the illness often associated with a pyrexia of 102° to 103°F. (38.9° to 39.4°C.). The tonsils are covered with a membrane which in appearance is difficult to distinguish from diphtheria and bleeding may occur if attempts are made to remove it. In rare cases the addition of a muco-purulent nasal discharge makes the differential diagnosis even more difficult. The throat clears slowly and swabbing often reveals infection with Vincent's organisms or streptococci. Most cases of glandular fever admitted to an infectious diseases unit are, in fact, admitted as possible cases of diphtheria. The clinical differential diagnosis depends upon three points. In glandular fever the temperature is still elevated on the ninth or tenth day of disease, the common time for admission, which it is not in diphtheria; the throat at this time compares in appearance with that of diphtheria on the third or fourth day of disease and the glands are small and discrete, whereas in diphtheria, owing to periadenitis in addition to adenitis, a firm mass is palpable rather than individual glands. The finding of glands elsewhere and in some cases an enlarged spleen are further suggestive signs of glandular fever.

Febrile type.—This is probably the most difficult of the three types to diagnose. It is characterized by an irregular pyrexia which may persist for

weeks. During the first week a macular rash very similar to the rash in rubella is seen in about a third of the cases. Headaches and sweats accompany the pyrexia. When the constitutional symptoms are subsiding enlargement of the glands may occur. The hæmatological picture is also late in developing. This type may have a very protracted convalescence and it is several months before the individual regains his normal health.

LABORATORY INVESTIGATIONS

The changes in the white blood count are the feature which is common in all these different clinical pictures. The total white count is usually raised to 12,000 to 15,000 per c.mm. and higher in some cases. There is a relative and absolute increase in the mononuclear cells with a fair percentage of monocytes. These changes often take some time to develop and early blood counts may not indicate the true nature of the illness. The appearance in the serum of the heterophilic antibodies to sheep's red blood corpuscles occurs usually in the first week in the glandular type, and often very much later in the febrile type. Tidy (1952) stressed the importance of the time relationship. A positive reading may be due to antibodies to horse serum which has been given previously, if, for example, diphtheria was suspected, and these can be absorbed by guinea-pig kidney before titration. A titre of 1:56 following absorption is usually accepted as diagnostic but some cases show positive results in much higher dilutions. As already indicated, a negative result does not exclude the condition and in some outbreaks, although clinically typical including the mononucleosis, not one may show a positive Paul-Bunnell test.

PROGNOSIS AND TREATMENT

The *prognosis* is very favourable, only a few deaths having been recorded in the world literature. In the main these were due to either a ruptured spleen or infective polyneuritis.

There is no specific *treatment* for the disease. Rest in bed is essential as in all febrile conditions. It has been stressed that in controlled series antibiotics have no effect on the virus but, when employed, may help any secondary infections particularly in the throat. A personal impression is that in the anginose type chlortetracycline often rapidly settles an elevated temperature.

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NOTES AND QUERIES

Tetanus Antitoxin

QUERY.—Is the giving of tetanus antitoxin to a person already immunized with tetanus toxoid a practice to be avoided and should the giving of a reinforcing dose of toxoid be preferred?

REPLY.—Tetanus toxoid is given to produce active and durable immunity against tetanus. A person who has received the usual primary course and reinforcing doses (if necessary) has tetanus antitoxin of his own manufacture in his circulating blood, and should not require, after a wound or injury, additional prophylactic antitoxin prepared in the horse. This is an advantage because any horse antitoxic serum, even when purified, may give rise to anaphylaxis or other unpleasant reactions; it may also induce the formation of precipitins, so that subsequent doses of serum may be eliminated too rapidly for protection to be adequate. Tetanus may therefore develop in spite of the usual prophylactic dose of antitoxin, and may cause death.

According to British Army practice, a person is considered to be 'immune':—

(1) For a period up to 6 months after two injections of tetanus toxoid—interval, 6 to 12 weeks.

(2) For a period up to 5 years after three injections of tetanus toxoid—intervals, 6 to 12 weeks, 6 to 12 months.

(3) For a period up to 5 years after a reinforcing dose of tetanus toxoid following a full primary course of three injections.

On wounding or injury, a reinforcing dose of 1.0 ml. of toxoid has been recommended as a precautionary measure, for actively immune persons in the above groups: *antitoxin is not required*. This toxoid boost is probably unnecessary and is often omitted if less than eighteen months, or perhaps two years, have elapsed since the third injection of the primary course or the last reinforcing dose. For additional information, an article by Parish, Laurent and Moynihan (*Brit. med. J.*, 1957, **i**, 639) may be consulted.

Fluid tetanus toxoid should *not* be given at the same time as tetanus antitoxin to a non-immune person, as has sometimes been suggested; partial neutralization of the toxoid may occur, thus reducing appreciably the antigenic response. It is also recommended that, in view of the disadvantages of repeated doses of horse serum, passive immunization after antitoxin should be followed routinely in six to eight weeks by a course of tetanus toxoid. This procedure is being adopted more widely.

H. J. PARISH, M.D., F.R.C.P.ED.

Severe Reactions Following Iron Injections

QUERY.—A patient of mine developed quite considerable staining after having 2 and 5 ml. of iron intramuscularly for the treatment of anæmia of pregnancy twelve months ago. She now gets considerable pain in these injection sites. Is this the result of fibrosis or of metallic foreign bodies in the tissues? Can I expect the pain and staining to go completely, or what otherwise is the best line of treatment to follow?

REPLY.—Although the incidence of severe reactions to intramuscular iron therapy is very low, less severe reactions such as staining of the skin can at times be troublesome, especially if the dose has been large at any one site, or if the injection site has been rather superficial. Occasionally the injected material can find its way along fascial planes and cause staining at some considerable distance from the injection site, however deep that may have been. When staining does occur it may last a very long time; indeed no assurance can be given that it will disappear completely. Insoluble iron complexes seem to be held in the tissues very much as products of hæmoglobin breakdown in erythema ab igne. Pain is not an invariable accompaniment of staining and is presumably due to some peculiarity in the local reaction to the pigment. Any treatment must be of the nature of a therapeutic experiment: local massage to improve local circulation and perhaps to expedite absorption of the foreign material can at least do no harm.

ALEXANDER BROWN, M.D., F.R.C.P.ED., F.R.F.P.S.G.

Snuff and Arterial Disease

QUERY.—Snuff-taking is recommended as an alternative to smoking. What are the physiological effects, if any, of the habit? Can it, for instance, be cheerfully countenanced in a patient with arterial disease of the limbs?

REPLY.—Tobacco snuff is ground tobacco with magnesia. Certain essential oils and sometimes menthol are added but the proportions are a trade secret. The nicotine content is from 0.3 to 1% and this is readily absorbed from the nasal mucosa. A person moderately addicted to sniffed tobacco uses about 1 g. daily (10 pinches of 0.1 g.) and so might absorb 3 to 10 mg. of nicotine. As 2 to 8 mg. of nicotine can be absorbed from the inhaled smoke of one cigarette, it is clear that, whilst the effects of a dose of nicotine are the same whether it is absorbed

from snuff or smoke, the dose ordinarily obtained is much less in the snuffer than the smoker. The practised snuff-taker does not allow the powder to enter beyond the nose, and so there are no chest complications, but nasal dermatitis could result. Snuff-taking is a good alternative to smoking for the tobacco addict, and its value in keeping the patient cheerful even though he has arterial disease of the limbs probably outweighs any possible ill-effects of small doses of nicotine.

C. ALLAN BIRCH, M.D., F.R.C.P.

Topical Application of Fluorine

QUERY (from a reader in New Guinea).—Our drinking water is rain water drained off the roof into 500-gallon tanks. I assume that it contains no fluorine. It would, I believe, be impossible to add fluorine to the water in the tanks so as to provide the optimum one part per million. We have two children aged 1½ and 2½ years. Would you advise giving the children fluorine either by oral tablets or by topical application? If so, what dosage do you advise? If the local application is advised, at what age should it be started, what preparation should be used, and how often should it be applied?

REPLY.—It should be remembered that, although the water supply is doubtless fluoride free, there are other sources of fluorine likely to be available in the diet. It would be interesting to know the distribution of fluoride-containing minerals in the area, or alternatively, an examination of representative vegetables in terms of fluorine content of their ash. Tea is a well-known source of fluorine for those who indulge freely in the habit. It is important that fluorine should not be regarded as a panacea and allowed to blind one to the fundamental need for sane dietary habits. In an area such as New Guinea one would have thought that fresh fruits and vegetables offered at the right time, that is, after the ingestion of sticky carbohydrates, would be the best insurance against stagnation of the latter, with its carious consequences.

Fluoride-containing dentifrices.—Jordan and Peterson of the Minnesota Department of Health have reported a tooth-brushing study in a group of 628 children. A dentifrice containing 0.4% stannous fluoride was used by 311 children and a control group of 317 at another school were given a dentifrice without stannous fluoride. The children brushed their teeth once a day under supervision. The first year's results show that the children using the stannous fluoride dentrifrice had 35% fewer D.M.F. (decayed, missing, filled) teeth than the controls. No new D.M.F. teeth were noted in 59% of the children using stannous fluoride dentifrice and in 44% of the controls. Urine samples from 40 boys in each group showed no increase in urinary fluoride levels as a result of the test dentifrice. This study confirms others on stannous fluoride dentifrices.

Topical application.—Muhler has reported on the clinical effectiveness of stannous fluoride which to be effective must be prepared fresh and used immediately. His method is to keep 0.4 g. of solid stannous fluoride in a 'Lilly No. 0' gelatin capsule, the capsules being kept in a container which is tightly sealed. The procedure is first of all to give a thorough prophylaxis, each tooth surface being cleaned and polished with pumice. Immediately before use the contents of one capsule (i.e. 0.4 g. solid stannous fluoride) are added to 10 ml. of distilled water. When completely dissolved the solution is immediately applied to the tooth. The 10 ml. is ample to treat the entire mouth, any residual solution being discarded. Before application one quadrant is isolated with cotton-wool rolls, the teeth are dried with air, and the solution is applied with a cotton applicator. The teeth are kept moist by repeated applications of the solution for 4 minutes, when the other quadrants are similarly treated. Three more treatments are usually given within 14 days. The series is usually started when the child is aged 3 and is maintained annually until the age of 6 years, after which treatments are recommended every two years. The lack of stability of stannous fluoride causes some workers to prefer the more stable sodium fluoride which has a long shelf life. McDonald and Muhler considered, however, that stannous fluoride is more effective than sodium fluoride in reducing caries in deciduous teeth, the comparative figures being 57% versus 21%.

PROFESSOR ERNEST MATTHEWS, D.I.C., PH.D., D.D.S., F.D.S., R.C.S.

Myxœdema and Hypercholesterolæmia

QUERY.—Seven months ago one of my patients developed early clinical signs of myxœdema. This was confirmed by two consultants following investigations in hospital which included blood cholesterol (which, of course, was abnormally high). In addition, she had clinical and radiological evidence of a post-pyloric ulcer. She has been treated on the usual dietetic lines for her peptic ulcer and later on, that is about a month ago, the consultant looking after her decided, in view of her previous hypercholesterolæmia, that meat, eggs, butter, cheese and other foods of animal origin should be excluded from her diet. This has naturally been most

unwelcome. As she is taking what appears to be an adequate quantity of thyroid, are these severe restrictions really necessary?

REPLY.—A patient who has myxœdema, but is receiving an adequate amount of thyroid, has been converted into the euthyroid state and hence the metabolism is, so far as we know, normal. There is therefore no rationale for treating her peptic ulcer on lines different from the treatment of an ulcer occurring in a patient otherwise normal. If she is receiving adequate treatment for her myxœdema her blood cholesterol should now be normal.

A. W. SPENCE, M.D., F.R.C.P.

Hazards of Diagnostic Chest X-rays

QUERY.—In Dr. Court Brown's article on 'The Hazards of Diagnostic X-rays' (*The Practitioner*, November 1958, p. 576) table I (p. 577) gives the gonad doses for chest x-rays as follows:—

	Male	*Female*
Chest (large film)	0.36 mr	0.07
Chest (M.M.R.)	0.25	0.15

As my work includes much chest radiology, I should be most grateful if you would confirm that the large film in fact gives more gonad radiation to the male and less to the female. If the figures are available I should also like to known the relevant gonad doses in chest screening per unit time at given Kv and milli-amps.

REPLY.—It is correct that a large chest film will give a greater dose to the male than to the female gonads, which in the case of the latter results in an appreciably greater loss of energy from the radiation beam by scattering as the beam passes through the tissues. No published figures are as yet available for the relevant gonad doses for chest fluoroscopy, per unit screening time, or for a range of physical characteristics of the beam.

W. M. COURT BROWN, O.B.E., M.B., D.M.R., F.F.R.

PRACTICAL NOTES

Antibiotics and Appendicitis

ACCORDING to R. B. Dietrick and his colleagues (*Annals of Surgery*, December 1958, **148**, 985), 'the early treatment of appendicitis with antibiotics masks the classical symptoms of the disease, makes the diagnosis more difficult, the disease more serious because of the additional time consumed, and increases both the morbidity and the hospital stay'. Of the 46 patients admitted to their hospital on account of appendicitis between January 1955 and April 1957, five had been treated with antibiotics or sulphonamides before a diagnosis was established. The average duration of symptoms in these five patients before admission to hospital was 12.5 days, compared with twelve to twenty-four hours for the others, and their average length of stay in hospital was 46.2 days compared with 10.4 days for the remainder. All five had severe complications. One, who nearly died, developed a severe wound infection and required a skin graft for an ulcer caused by extravasation of noradrenaline, and was subsequently readmitted on account of an abscess in his operation scar. Another developed intestinal obstruction due to a volvulus about the point of adherence of the inflamed appendix to the terminal ileum, whilst a third developed persistent stenosis of the rectum at the site of adhesion of the appendix to the rectum. Yet another was readmitted on account of intestinal obstruction due to postoperative adhesions. The authors recommend that 'in patients admitted with abdominal pain in whom the symptoms are atypical, the examining physician should have a high index of suspicion that the patient may have received antibiotic therapy and should closely question the patient concerning this possibility'.

Promethazine in Obstetrics

As a result of their experience in over 7,500 confinements, J. J. Carroll and his colleagues, of Vancouver, B.C. (*Journal of the American Medical Association*, December 27, 1958, **168**, 2218), recommend a combination of pethidine and promethazine on the grounds that it 'provides superior sedation-analgesia and is attended by greater safety than is the use of pethidine alone'. The usual dosage schedule was to give 25 to 50 mg. of promethazine and 50 mg. of pethidine intramuscularly when the patient began to complain unduly of her discomfort. The dose was repeated at the discretion of the labour room nurses or according to the instructions of the obstetrician. For the individual patient the total dosage of promethazine ranged from 25 to 150 mg. (average 56.5 mg.) and of pethidine from 25 to 200 mg. (average 93.7 mg.). The results are summed up as follows: 'Ninety-five per cent. of the viable infants cried spontaneously within one minute of delivery. Resuscitation is almost never necessary, and the use of narcotic antagonists has been almost eliminated'. It is also claimed that 'morbidity in the new-born infant from pulmonary complications, especially atelectasis and

pneumonia, showed a significant decrease'. Further, 'the elimination of apprehension not only has reduced the discomfort of the patients but . . . has lessened the tenseness, fatigue, and irritability of the nurses in charge'.

Renal Function Tests in Prostatic Obstruction

THE blood urea or its equivalent and intravenous pyelography are the standard useful tests in prostatic obstruction, according to Professor C. A. Wells (*Annals of the Royal College of Surgeons of England*, January 1959, **24**, 21). The former is not a very sensitive test and a normal figure may be obtained in the presence of quite marked disturbance. In other words, a raised blood urea means that 'something is definitely wrong'. In general the following figures may be taken as reliable guides in prostatic obstruction:—

Up to 40 mg.%.—Unlikely to be much renal damage and complete recovery probable.

40 to 60 mg.%.—Unlikely to be much renal damage and complete recovery probable—but less certain.

60 to 80 mg.%.—Hydronephrosis almost certain. Some degree of renal damage probable.

80 mg.% and over.—Some degree of renal damage highly probable.

150 to 250 mg.%.—Renal damage almost certain. Complete recovery highly improbable. Condition almost certainly neglected.

Over 250 mg.%.—Condition certainly neglected and of long standing. Acidosis, anæmia and œdema all highly probable. Complete recovery of renal function almost out of the question.

Intravenous pyelography is probably quite safe whatever the blood urea, and should be carried out whenever possible in prostatic obstruction. Amongst its advantages are that the density of the bladder shadow gives an indication of total renal function even when the kidneys cannot be well visualized and the size of the bladder shadow after micturition is a guide to the amount of residual urine. In addition, progress can be observed after operation in the shrinkage of hydronephrosis and the disappearance of residual urine.

Penicillin and Aortic Aneurysm

SATISFACTORY results are reported by R. Ward and L. Read (*British Journal of Diseases of the Chest*, January 1959, **53**, 52) from the use of penicillin in the treatment of advanced syphilitic aortic aneurysm in 13 patients, whose ages ranged from 55 to 75. All had positive serological reactions for syphilis. Four of the patients had also aortic incompetence and three showed evidence of neurosyphilis. In the earlier stages of the investigation the patients were given potassium iodide, 60 grains (4 g.) daily, for three weeks before starting penicillin, but this practice was soon discontinued, and patients were started off on penicillin: 600,000 units of procaine penicillin daily until a total of 20 mega units had been given. This constituted the complete treatment and the course was not repeated. Two patients had Herxheimer reactions, with sudden 'collapse', fall of blood pressure and associated weakness. Both recovered within a few hours, and penicillin was continued the next day. In neither case was there any electrocardiographic evidence of myocardial infarction. In a follow-up period of 32 to 74 months, three of the patients have died, one is subject to attacks of left ventricular failure, and nine are leading relatively normal lives. None of the deaths was due to rupture of the aneurysm: two of the patients were in their seventies and the third had aortic incompetence.

Rectal Function in Paraplegics

'A SATISFACTORY bowel regime can be achieved in the spinal man, wherever the lesion' is the conclusion of L. Guttmann (*Proceedings of the Royal Society of Medicine*, February 1959, **52**, 86), based upon a study of over 1,900 paraplegic patients treated at Stoke Mandeville over a period of fifteen years. It is emphasized that 'a regime ensuring regular and efficient bowel action once every twenty-four hours is as much an individual matter in the spinal man as in the normal person'. Although enemas may be necessary during the stage of spinal shock, as this stage passes a conditioned reflex defæcation should be instituted at a regular time each day —preferably after a meal when the gastro-colic reflex can be utilized as an initiator of reflex defæcation. To facilitate this regularity, it is important to keep the bowel contents in such a condition that the stool reaches the rectum firm but soft. This is done by appropriate diet and mild laxatives or glycerin suppositories. The patient must also be trained to use certain stimuli to elicit defæcation: e.g. digital stimuli of so-called trigger zones in the sacral area—with or without massage or gentle rubbing of the abdomen, or change of respiratory rhythm to increase the intra-rectal pressure.

Salt-deficiency Heat Exhaustion

IN a review of their findings in 59 cases of salt-deficiency heat exhaustion which occurred among oil-tanker crews in the Persian Gulf during the summer months of 1956 and 1957, C. S. Leithead and his colleagues (*Annals of Tropical Medicine and Parasitology*, December 1958, **52**, 456) note that the clinical features included fatigue, headache, giddiness, nausea,

vomiting and muscle cramps. The blood urea was high in the five cases in which it was investigated, and attention is drawn to the 'still common error' of mistaking this for a sign of renal disease. It is emphasized that 'salt-depletion heat exhaustion, in common with most of the other heat disorders, occurs most frequently in short-term visitors to hot climates —particularly if, like Service personnel and mercantile crews, they have to work hard from the moment of entry'. As a preventive measure, for men in ships visiting tropical waters a minimum of 20 grammes of salt is recommended daily for upper-deck workers and 30 grammes daily for engine-room staff and commissariat personnel. As the average meat-containing diet contains around 10 grammes daily, the additional salt must be added at table. Some individuals find such additions unpalatable, or even nauseating, even if disguised in such vehicles as soups or tomato juice. In these cases the extra salt can be taken in the form of enteric-coated tablets, each containing 0.65 g. of iodized sodium chloride. A warning is given, however, that such tablets do not dissolve readily in the intestines and they are therefore unsuitable for treatment of an established case.

Formaldehyde Fumigation

THE 'capabilities and limitations' of formaldehyde as a disinfectant are set out in a report in the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* (December 1958, **17,** 270). It has the advantages of being cheap, easy to handle and of not being injurious to fabrics, paints, or metals, and of being rapidly neutralized by ammonia. Further, its pungent and irritating odour gives adequate warning of its presence at concentrations (5 p.p.m.) too low to be toxic. It is pointed out that air containing more than 7% formaldehyde is a potentially explosive mixture but such concentrations are never likely to be produced during fumigation. For formaldehyde to act as a disinfectant it must dissolve, at adequate concentration, in a film of moisture in the immediate vicinity of the organisms to be killed. For most purposes the gas is best generated by boiling a mixture of commercial formalin with that amount of water necessary to ensure adequate humidity. There are three applications for which formaldehyde is the most suitable means of disinfection: (i) Rooms from which fabrics have been removed. (ii) Small objects which cannot be heated or wetted without damage, such as respirators, leather goods, boots, and toys not made of fabric. (iii) Mattresses and woollen blankets. If these are spread out to allow access of the gas, surface disinfection is possible at room temperature, but if disinfection of the interior of the mattress or of folded blankets is required, some form of heated chamber must be used.

Bull-fiddle Hand

'BULL-FIDDLE hand' is the name given by G. D. Campbell (*South African Medical Journal,* January 3, 1959, **33,** 20) to a new occupational hazard of musicians. 'Bull-fiddle' is the name given in jazz circles to the large string instrument more conventionally described as the 'bass' or 'double bass'. It has four strings, the largest of which are tightly wound round with steel wire, whilst the other two are made of naked gut. It is played solely by striking or plucking the strings, and it has been estimated that in the course of an evening's playing the strings may be struck or plucked several thousand times. It is this repeated trauma that is responsible for 'bull-fiddle hand'. In the milder cases there is blistering, leading on to callosity formation, of the skin overlying the flexor aspects of the terminal phalanges of the right index and middle fingers and the radical surface of the proximal and distal interphalangeal joints. In more advanced cases there is a tenosynovitis of the tendon sheaths of the extensors of the right index and middle fingers. This causes a tense swelling over the dorsum of the right hand, resulting in considerable discomfort and limitation of movement of the hand and wrist.

Intrathecal Hydrocortisone

THE intrathecal injection of hydrocortisone is recommended for the relief of otherwise intractable pain arising from malignant metastases in the spine, by J. M. Grappe and A. Sacrez in an article in *Strasbourg Médical* (1958, **9,** 488) which is summarized in *La Presse Médicate* (January 3, 1959, **67,** 18). Details are given of three patients—two with carcinoma of the prostate and one with carcinoma of the lung—in whom this method brought relief. In all three the metastases were in the lumbar region. The hydrocortisone was given in either the lumbar or suboccipital region. The needle having been inserted, 3 or 4 millilitres of cerebrospinal fluid are allowed to escape. A syringe, containing 50 to 75 mg. of hydrocortisone dissolved in 2 to 3 millilitres, is then attached to the needle, and an equal volume of cerebrospinal fluid is slowly withdrawn into the syringe to dilute the hydrocortisone solution. The diluted solution is then injected slowly. It is claimed that relief of pain was obtained within a period ranging from a few hours to one or two days, and that this persisted for about a week, when a further injection is called for and is said to be equally effective. No untoward reactions have been encountered while using this procedure.

REVIEWS OF BOOKS

A Clinical Introduction to Heart Disease. By CRIGHTON BRAMWELL, M.D., F.R.C.P. London: Oxford University Press, 1959. Pp. 229. Figures 61. Price 21*s*.

MOST physicians involved in the teaching of medical students are deeply concerned by their consciousness of the defects in our present system of instruction. The contrast between the eager young student, fresh from his three-year apprenticeship in pre-clinical basic science, and the frequently dull, bewildered and confused candidate at the final clinical examinations is sufficiently striking to provoke heart searching among those responsible for his teaching. Whilst part of the responsibility for the confusion and apathy lies with those who arrange the overcrowded curriculum, a goodly share rests on the teachers of medicine. In the students' eyes the arid pages of the average systematic textbook seem too often divorced from clinical realities.

There is room therefore for books such as this, in which a master of his subject attempts a synthesis of systematic and clinical approaches. Crighton Bramwell is particularly well fitted for the task. He served a distinguished and fruitful apprenticeship in the study of the physiology of the circulation, and in his subsequent career as a clinician and teacher of medicine and of cardiology has amassed a vast clinical experience. What such a man distils out of his twin disciplines must command respect.

The book is specifically intended for students and general practitioners. The aim has been to present an intelligible approach to the cardiac patient based on physiological principles and clinical experience. In this it has succeeded admirably. Lucid, free from dogma and permeated with common sense the book is one which will help the student confronted by the clinical mysteries of his ward work and will at the same time give to practitioners a succinct account of up-to-date clinical cardiological practice. A noteworthy feature is the emphasis on the human values which must inspire the efficient no less than the sentimental physician. There is much clinical wisdom in its pages.

Leprosy in Theory and Practice. Edited by R. G. COCHRANE, M.D., F.R.C.P., D.T.M. & H. Bristol: John Wright & Sons Ltd., 1959. Pp. xv and 407. Figures 189. Price 84*s*.

EVERY now and then a textbook appears which constitutes a landmark in our understanding and control of disease. Such a book is Dr. Cochrane's 'Leprosy in Theory and Practice'. With the aid of twenty-three collaborators—all experts in their respective fields and drawn from all five Continents—he has produced the most comprehensive and authoritative textbook on leprosy which has yet been published. As Sir George McRobert points out in his foreword: 'All aspects of this most fascinating disease have been brought into this comprehensive book by one who has been outstanding in this generation for his impact on the disease from both the scientific and religious angles'.

The hallmark of this book is its breadth of vision. For too long leprosy has been looked upon as a misfortune of mankind with certain unpleasant sociological connotations and primarily the concern of religious and philanthropic organizations. What Dr. Cochrane has done is to persuade clinicians and research workers that it is a disease which affects the whole body and that to be successful any attempt to understand its workings and try and find a satisfactory means of treatment requires the skills of practically all branches of medicine and surgery. Thus, in this volume Dr. Graham Weddell, of Oxford, discusses the sensory and neurohistological changes in leprosy, Dr. E. M. Brieger, of the Strangeways Research Laboratories, Cambridge, contributes a chapter on the submicroscopical structure of *M. lepræ*, and Dr. R. W. Riddell, of the Brompton Hospital, reviews the acid-fast bacteria. Equally important, the book is a happy blend of the theoretical and the practical. The clinician will find it as valuable as the research worker. Indeed, he will go far before he finds a more useful guide in dealing with his patients with leprosy. All that remains to be said is that the book is admirably produced with a wealth of beautifully reproduced illustrations in colour as well as black and white.

Brain, Memory, Learning. By W. RITCHIE RUSSELL, C.B.E., M.D., D.SC., F.R.C.P. Clarendon Press: Oxford University Press, 1959. Pp. xii and 140. Figures 12. Price 18*s*.

FOR too long the neurologists, with certain notable exceptions, have tended to look upon their specialty as merely a means of localizing the lesion in a patient whose nervous system was obviously out of order. Similarly they have given the impression that they looked upon the brain as little more than a gloriously complex telephone exchange for emitting and receiving messages to and from the various parts of the body. The advent of the neurosurgeon and of

the neurophysiologist, with his instruments of increasing precision, is changing all this, and neurologists are now evincing an increasing interest in the mechanism of the brain and its relationship to memory and learning.

Dr. Ritchie Russell has been one of the pioneers in this field, and in this admirable brief book he has reviewed the available data and—most important of all—has not been afraid to discuss the implications in such practical fields as education and the bringing up of children. Needless to say, many neurologists will disagree with him, but that need not worry the non-specialist—the general practitioner and the general consultant. It is always stimulating, often provocative, but never dull. Written in a concise, but never complicated, style, it holds the reader's attention from beginning to end. This is one of the few books of which it can honestly be said that no clinician worth his salt can afford to miss reading it. He will learn a lot—above all it will make him sit up and think.

Neoplastic Disease at Various Sites: Vol. II. *Tumours of the Bladder.* Edited by DAVID M. WALLACE, O.B.E., M.S., F.R.C.S. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. xvi and 352. Figures 202. Price 60*s.*

IN this second volume in a series of monographs on neoplastic diseases the editor has had the assistance of thirteen other contributors. The pathological aspect is well dealt with by Dr. Cuthbert Dukes and Dr. R. C. B. Pugh. This section is profusely and beautifully illustrated both in regard to actual specimens and to the microscopic structure of tumours in their varying grades. There is a valuable section by Mr. C. I. Cooling dealing with the sites of metastases and the causes of death in a series of cases confirmed at post-mortem examinations. Not the least interesting section is that by Professor Boyland on the etiology of bladder tumours and the role of enzymes in carcinogenesis.

The clinical assessment by the editor is a most important part of the book. He rightly insists that, as well as cystoscopy, there must be a complete radiological survey, a histological examination of a biopsy specimen and a bimanual examination under full anæsthesia. Even when all the known means of diagnosis and assessment are employed, it can be difficult to know which is the best method of treatment. The section on the surgery of bladder tumours is concise and is a description of the editor's own practice, which has a strong bias towards radiotherapy. Indeed, in almost every case treated, some form of irradiation is considered the first line of attack. The methods of application of radiotherapy are clearly and succinctly dealt with by Professor Smithers, Dr. McKay and Mr. Wallace. Finally, there is an excellent section on the analysis of treatment in 1,420 cases, each of which was clinically graded and carefully annotated.

This is a very good book, beautifully produced and well illustrated. Stimulating and occasionally controversial, it contains an immense amount of factual knowledge, and some interesting surmises. Every urologist, and every surgeon who deals with bladders, should read it and read it all.

Infectious Diseases of Children. By SAUL KRUGMAN, M.D., and ROBERT WARD, M.D. London: Henry Kimpton, 1958. Pp. 340. Illustrations 51. Price 75*s.*

THE scope of this admirable book is in some ways wider than the title suggests, as adult symptoms are always given when they differ from those usually found in children and treatment schedules similarly embrace all age-groups. On the other hand, certain infections such as brucellosis, leptospirosis and gastroenteritis of infants are omitted. The arrangement follows the accepted textbook pattern except that the diseases are in alphabetical order. There are good chapters on Coxsackie and herpes simplex infections and up-to-the-minute information on such things as mumps vaccine and the adenoviruses. Although, according to the authors, intended for 'pædiatricians, general practitioners and medical students', the latter might find the rather terse style a little difficult to read in large doses, but this should be more than compensated for by the very clear and helpful illustrations. Most British authorities would deprecate the omission of intrathecal penicillin from the treatment of pneumococcal meningitis, but apart from this there are obviously no major differences in therapy of infectious diseases on the two sides of the Atlantic.

This beautifully produced book can be thoroughly recommended as a practical up-to-date reference for anyone dealing with infections.

Convulsive Disorders of Children. By DORA HSI-CHIH CHAO, M.D., RALPH DRUCKMAN, M.D., and PETER KELLAWAY, A.M., PH.D. Philadelphia and London: W. B. Saunders Co., 1958. Pp. vi and 151. Figures 25. Price 42*s.*

THE authors have summarized their experience at the Blue Bird Clinic in Houston, Texas, since 1949. The subject is considered in fifteen chapters, most of them brief, and is discussed in a general way. Illustrative case histories are included. No statistics are offered in support of the statements and recommendations made and

whilst this didactic presentation is admirable for undergraduate purposes it will tend to restrict the wider use of the book. References are given at the end of some of the chapters but are not referred to in the text. Convulsions in the neonatal period are not considered and in view of the brevity of the book it is surprising to find four chapters devoted to general aspects of seizures and one to 'Epilepsy in adult life'. The chapter on electroencephalography is, as might be expected, an authoritative summary of the significant findings and uses of the procedure.

Within the limitations mentioned, the book provides an acceptable and up-to-date summary of the subject for those with an interest in the problems of convulsions in childhood.

The Management of Childhood Asthma. By FREDERIC SPEER, M.D. Oxford: Blackwell Scientific Publications, 1958. Springfield, Illinois: Charles C Thomas. Pp. xii and 116. Illustrated. Price 36*s*.

THIS monograph from Kansas City is a well-balanced account of a difficult subject. The author starts wisely with a chapter on the asthmatic child and his family, and his general approach throughout is that of an experienced pædiatrician who is concerned to help the child rather than merely treat asthma in children. As is usual in books from the United States the sections on pollens and foods are not directly applicable in the United Kingdom but the diets could be easily adapted and it is a pity that the whole chapter on allergic cooking was not rewritten for the British reader (as the cost of the book is relatively high this seems a modest request). It is surprising that the use of cortisone in asthma (other than in status asthmaticus) is not considered more fully.

Cancer. Volume IV. Edited by RONALD W. RAVEN, O.B.E., T.D., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1958. Pp. ix and 555. Figures 173. Price 85*s*.

THIS fourth volume is devoted entirely to 'clinical aspects of malignant tumours'. The opening chapter is devoted to 'The staging of cancer', whilst the remaining thirty-three deal with the disease according to the site. The twenty-nine contributors are mainly drawn from the London teaching hospitals. In the attempt to be comprehensive, a certain sense of balance is lacking. Thus, as much space is devoted to cancer of the heart and blood vessels as to cancer of the trachea, bronchus, lung and pleura. There is also a tendency for at least some of the authors to ignore newer work. This is particularly noticeable in the chapter on cancer of the urinary bladder. The task of the reviewer is not made easier by the piecemeal way in which the book is being published. Thus, on p. 191 the use of intracavitary irradiation in the treatment of tumours of the bladder is dismissed by the comment: '(see Vol. 5)', whilst in the section on the treatment of acute leukæmia the reader is informed (p. 433): 'No description is given here of the details of chemotherapy in acute leukæmia as this is fully described in Volume 6'.

Once the entire book is published it will be easier to assess its real value. Meanwhile all that can be said about this volume is that it provides a useful summary of the essentials of our present knowledge of the subject.

Symposium on Nuclear Sex. Edited by D. ROBERTSON SMITH, M.D., and WILLIAM M. DAVIDSON, M.D. London: William Heinemann Medical Books Ltd., 1958. Pp. xvii and 188. Price 21*s*.

THIS well-presented account of a conference held in London in 1957 contains a valuable amount of data presented by many experts in the field of genetics, embryology and endocrinology. Barr's original demonstration of sex chromatin in resting nuclei of female cells has been exploited skilfully in the study of intersex and varieties of hypogonadism. This book affords an excellent insight into the current work and should be read by all biologists and doctors concerned with the problems of sex. The significance of sex chromatin is described most admirably, but those concerned in demonstrating the presence or absence of the chromatin mass would have welcomed more discussion on the technical aspects of the matter. It is not easy to be certain whether a cell is genetically male or female and good results require considerable experience and elegant staining technique. Readers of this book, however, will be made aware of just what genetic sex entails and its relationship to those more practical entities, maleness and femaleness.

A Doctor Looks at Miracles. By HARLEY WILLIAMS. London: Anthony Blond, 1959. Pp. 232. Price 16*s*.

'To affirm, in this sceptical and materialistic century, *I believe in miracles*, will seem to many people a romantic hangover from an age of faith'. 'A miracle is a fragment lifted out of the timeless chaos of unrecorded happenings, to become, for one brief instance, an episode in the life of time'. These are the opening and the concluding sentences of Dr. Harley Williams' new book. In between he covers a vast amount of ground ranging from the Resurrection, through Buddhism, Mesmerism, Christian

Science and Lourdes, to extrasensory perception.

It is a fascinating book, but in his attempt to be impartial the author tends to lose himself in a mirage of words. His chapters on the miracles of Jesus and the Resurrection and that on St. Francis of Assisi are models of their kind—reverent yet keenly analytical. In dealing with the mystics of the East, however, he tends to get out of his depth and his handling of Christian Science and Lourdes is disappointing. To many readers, however, the most disappointing feature of the book will be the failure to explore the potentialities of extrasensory perception in this field. The major obstacle, of course, in the way of attempting to discuss miracles is that they are entirely a matter of belief. Once a miracle has been rationalized it is no longer a miracle. So often the miracle of today is the accepted fact of tomorrow. What we have achieved today is a much better understanding of the influence of mind over body. Is it possible that when we attempt to explore matters of the spirit we are trespassing on territory which is for ever beyond the veil so far as the searching mind of mortal man is concerned?

NEW EDITIONS

Diseases of Women, by Ten Teachers, under the direction of Frederick W. Roques, M.D., M.CHIR., F.R.C.S., F.R.C.O.G., in its tenth edition (Edward Arnold (Publishers) Ltd., 36*s*.) maintains the high standards which have characterized this work since it first saw the light of day forty years ago under the editorship of Sir Comyns Berkeley, Russell Andrews and J. S. Fairbairn. Contributors may come and go—in the preparation of this edition Mr. Brian Evans has taken the place of Mr. Arthur Bell—but the old traditions of sound judgment, discrimination and clinical acumen remain unaltered. Among the many changes in this edition are the inclusion of a section on vaginal cytology and radical revision of the chapters on tuberculous salpingitis and prolapse.

A Short Practice of Surgery, by Hamilton Bailey, F.R.C.S., F.A.C.S., F.R.S.E., and McNeill Love, M.S., F.R.C.S., F.A.C.S. (H. K. Lewis & Co. Ltd., 84*s*.).—The eleventh edition of 'Bailey and Love' is longer by three hundred and sixty pages than the tenth, and it has nearly three hundred more illustrations. It has two new chapters on fluid balance and on the principles of radiotherapy. Many of the other chapters have been rewritten, for the most part by Hamilton Bailey, whose attractive style and genius for apt illustration are largely responsible for the secure place that this book has established for itself among surgical students and postgraduates.

A Handbook of Medical Hypnosis, by Gordon Ambrose, L.M.S.S.A., and George Newbold, M.B., B.S., M.M.S.A., D.R.C.O.G., D.C.H., in its second edition (Baillière, Tindall & Cox, 27*s*. 6*d*.) provides a useful practical guide to the subject for the general practitioner. The section on the technique of induction has been amplified and the chapter on the neuroses has undergone considerable revision. Although the authors are obviously enthusiasts, they have produced a commendably balanced book on the subject.

Poisoning: A Guide to Clinical Diagnosis and Treatment, by W. F. von Oettingen, M.D., PH.D., in its second edition (W. B. Saunders Co., 87*s*. 6*d*.) preserves the original form. Some 400 of the 600 pages are devoted to descriptions of the symptoms and treatment of named poisonings. Statements are now included on toxic reactions short of gross poisoning. Part 2 consists mainly of lists of drugs causing particular symptoms such as perspiration and is not of great value. A useful chapter is one on laboratory tests for the relatively few poisons identifiable in blood and urine. Some of the advice on treatment is vague and would leave the reader without explicit instructions in an emergency. This book has a place on the reference library shelf, but at this price it will not replace the smaller books giving more detailed and dogmatic instructions about common poisonings.

Medicine for Nurses, by M. Toohey, M.D., M.R.C.P., D.C.H., in its fourth edition (E. & S. Livingstone Ltd., 30*s*.) looks much the same as its predecessors, but it has been thoroughly revised. Nurses will appreciate the excellent diagrams and also a new chapter entitled 'Points to Remember' in which twenty topics including the toxic effects of common drugs are discussed. The book is beautifully produced and well deserves its popularity.

BINDING CASES

Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 6*s*. each, post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 15*s*. per volume; this includes the cost of binding case and return postage.

The contents of the April issue, which will contain a symposium on 'Emergencies in General Practice,' will be found on page A 122 at the end of the advertisement section.

Notes and Preparations see page 391.
Notes from the Continent see page 395.
Fifty Years Ago see page 397.
Motoring Notes see page A 97.
Travel Notes see page A 101.

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Anaesthesia, 1957, *12*, 174

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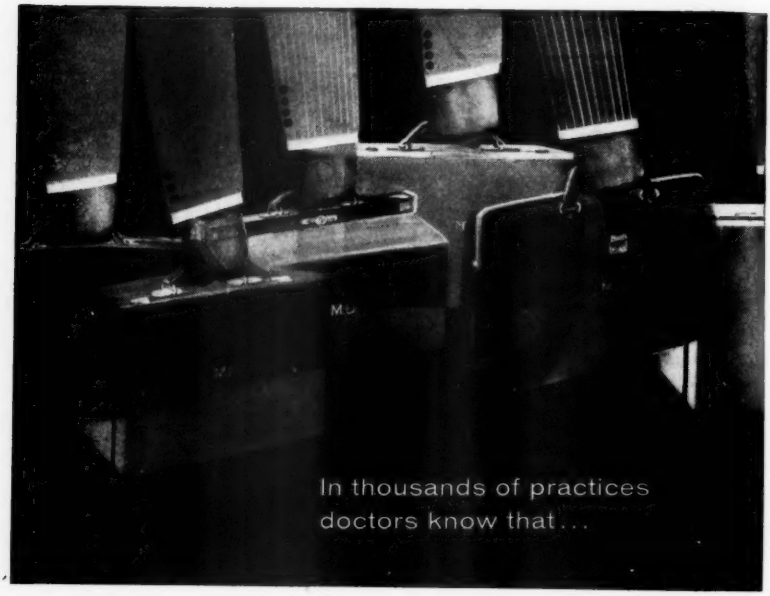

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NOTES AND PREPARATIONS

NEW PREPARATIONS

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'CORANGIL' tablets consist of a citrus-flavoured outer coating containing 1/130 grain (0.5 mg.) of glyceryl trinitrate, and an inner core containing ½ grain (20 mg.) of pentaerythrityl tetranitrate, 2 grains (120 mg.) of dihydroxypropyl theophylline, 2 grains (120 mg.) of magnesium trisilicate, B.P., and 1 grain (60 mg.) of papaverine hydrochloride B.P. They are indicated 'for the prevention and treatment of angina pectoris, and the promotion of coronary dilatation following myocardial infarction', and are said to provide immediate relief in the acute attack. Issued in bottles of 50, 250 and 1000 tablets. (Allied Laboratories Ltd., 140 Park Lane, London, W.1.)

'DISTOLYT' tablets each contain 10 mg. of chlorcyclizine hydrochloride and 100 mg. of guaiacol glyceryl ether, a combination which, it is stated, 'facilitates expectoration of tenacious mucus and reduces the frequency of excessive unproductive cough'. Issued in tubes of 24 and bottles of 100 sugar-coated tablets. (The Distillers Co. (Biochemicals) Ltd., Broadway House, The Broadway, Wimbledon, London, S.W.19.)

'IVAX' is a pleasantly flavoured liquid preparation, each fluid ounce (28.4 ml.) of which contains 4 g. of sulphaguanidine B.P., 300 mg. of neomycin sulphate B.P., and 6 g. of light kaolin B.P. It is indicated for the treatment of bacillary dysentery, food-poisoning and specific and non-specific diarrhœas, and 'quickly consolidates the stools, suppresses the infecting organisms and soothes the irritated mucosa'. Issued in bottles of 6 fluid ounces. (Boots Pure Drug Co. Ltd., Station Street, Nottingham.)

'MEZURAN' tablets each contain 0.5 g. of sulphadimidine and 0.05 g. of phenylazo-diaminopyridine hydrochloride, and are intended for the treatment of urinary-tract infections due to organisms which are susceptible to sulphonamide therapy. They are said to provide prompt symptomatic relief from pain and frequency, thus making the patient comfortable during treatment. Issued in containers of 25 and 500. (Imperial Chemical Industries Ltd., Pharmaceuticals Division, Fulshaw Hall, Wilmslow Cheshire.)

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'ZYNOCIN' lozenges each contain 1 mg. of xanthocillin and 5 mg. of benzocaine and are said to be effective against the gram-positive and gram-negative organisms found in the majority of infections of the respiratory tract. Issued in tubes of 12 lozenges. (The Distillers Co. (Biochemicals) Ltd., Broadway House, The Broadway, Wimbledon, London, S.W.19.)

ROYAL SOCIETY OF MEDICINE

THE next meeting of the Section of General Practice will be a combined meeting with the Section of Endocrinology and will be held at 8.15 p.m. on Wednesday, March 18, 1959. The subject for discussion will be 'The Diagnosis of Thyroid Disease' and the opening speakers will be Professor E. J. Wayne and Drs. D. P. Wheatley, A. G. Macgregor and D. N. Baron.

TRAVELLING FELLOWSHIPS

The College of General Practitioners invites applications from members of the College for the 1959 *Upjohn Travelling Fellowships*. Not less than fifteen fellowships of up to £200 each will be awarded to members practising in the United Kingdom or Eire who have not previously been awarded an Upjohn fellowship. The purpose of the fellowships is to enable general practitioners to carry out a minimum of two weeks' post-

graduate study at their old teaching hospitals or at any other hospitals, clinics, health centres or general practices of their choice in the United Kingdom and Eire. Application forms, which must be submitted before August 1, 1959, may be obtained from the Secretary, College of General Practitioners, 41 Cadogan Gardens, London, S.W.3.

COURSES AND CONFERENCES

Fundamental and Practical Aspects of Diabetes will be the subject of a course organized by the Postgraduate Medical School of the University of Cambridge, to be held at Addenbrooke's Hospital, Cambridge, on April 16, 17 and 18, 1959. Full details may be obtained from the Secretary, The Medical School, Tennis Court Road, Cambridge.

The Chronic Rheumatic Diseases will be the subject of a concentrated weekend course, with lectures, ward rounds and practical demonstrations, to be held at the Rheumatism Unit of St. Stephen's Hospital, Fulham Road, Chelsea, London, S.W.10, on March 14 and 15, 1959. Full details may be obtained from the Secretary, Fellowship of Postgraduate Medicine, 60 Portland Place, London, W.1.

POLIOMYELITIS VACCINATION

Over 12 million children and adults have not yet taken advantage of the poliomyelitis vaccination scheme, according to a statement issued by the Ministry of Health. Although the acceptance rate for children up to the age of 15 is mounting, both it and the response from expectant mothers are far from satisfactory. It is in the case of the age-group 15 to 26 years, however, that the position is most unsatisfactory, the acceptance rate for this group being only 6%. It is stated that 'there are at present ample supplies of vaccine—over 20 million doses have been issued since the start of the scheme, including those issued up to the end of January—and there is reasonable hope of steadily expanding British production'.

WELSH ENTERPRISE

As Dr. A. W. Franklin pointed out in his article on 'Recent changes in the care of the newborn' in our January issue, 'routine urine tests for phenylpyruvic acid may rescue a child from the mental defect and epilepsy of phenylpyruvic oligophrenia (phenylketonuria) with the help of a phenylalanine-low diet'. Although only about 1% of cases of mental deficiency are attributable to phenylketonuria, the fact that it can be prevented if discovered early enough is ample justification for taking every reasonable care to detect it before irreparable damage has been done. This can be achieved quite easily by examining the urine for phenylpyruvinate acid, which can be detected after the third week of life. With commendable enterprise, Dr. W. Powell Phillips, the medical officer of health for Cardiff, has established a routine urine-testing service, so that all babies born in Cardiff may be tested for this purpose.

DENTAL MANPOWER

The United States has the highest ratio of dentists to population—1:1,900. Sweden comes next with 1:1,550. At the other extreme is Indonesia, with 1:270,000. Other comparable figures are 1:3,792 for the United Kingdom, 1:2,250 for Australia, and 1:10,800 for South Africa. These are some of the facts presented to the WHO expert committee on auxiliary dental personnel, which met recently in Geneva. According to the committee, 'the least difficult and the least expensive although still efficient way of dealing with this situation is to train more auxiliary dental personnel to enable the dentists to render a greater amount of service to a greater number of people'.

FLUORIDATION AND CARIES

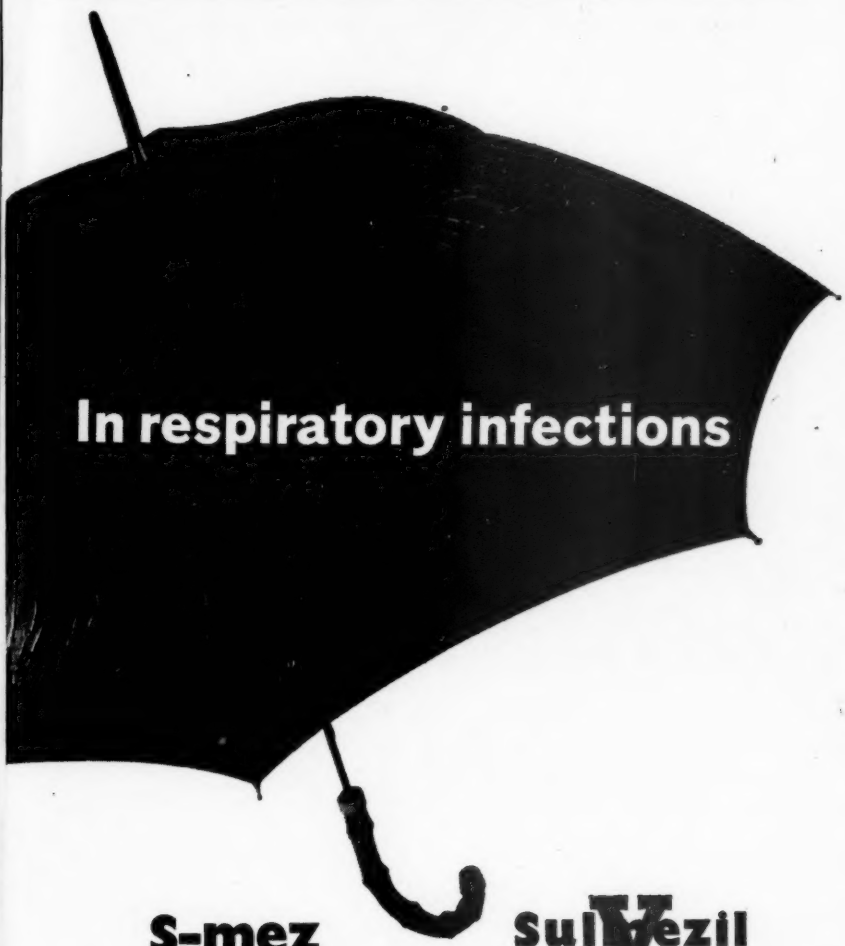
The results of four years' fluoridation of the public water supply is described by the health commission of Philadelphia as 'truly amazing', according to a report in the *British Dental Journal* (1958, **105**, 430). A study of 17,617 six-year-old children in 1954-55, compared with one of 21,834 of similar age in 1957-58, showed a decrease of nearly 50% in the caries rate and of 43% in extractions.

SCABIES IN SCOTLAND

Scabies is on the increase in Scotland, according to W. N. Boog Watson (*Med. Offr*, 1958, **100**, 293). The incidence in school children has risen from 0.6 per 1000 in 1953-54 to 2.4 per 1000 in 1956-57. This increase has resulted almost entirely from the increase in Edinburgh (0.7 to 1.9 per 1000) and Glasgow (1.3 to 8.3 per 1000). The reason for drawing attention to this increase is that scabies has been so relatively rare that teachers have been finding difficulty in obtaining cases to demonstrate to their students. The result is that many of the younger generation of practitioners are not familiar with the disease and may therefore be liable to miss a case in the early stage when efficient treatment will not only eradicate the infection but reduce the risk of its spreading to other members of the family.

NUTRITIONAL PROBLEMS OF AFRICA

The nutritional problems of Africa are as variegated as its fauna. A recent WHO report,



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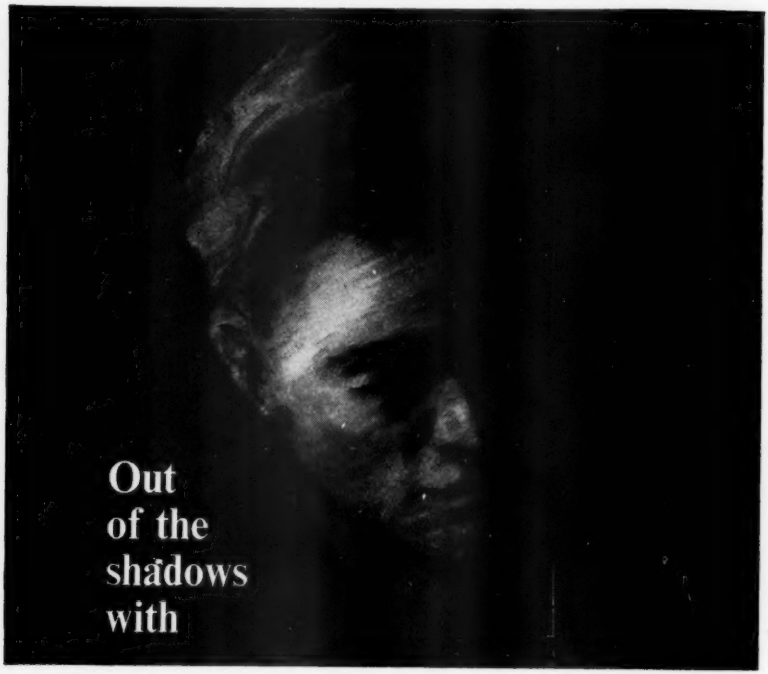

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for instance, notes that in Mauritius rice is prepared by washing it vigorously in several changes of water which is later discarded, and finally rinsing it in water before serving it at a meal. Investigations have shown that this depletes the rice of up to 70% to 80% of its iron and vitamin content. In view of the high incidence of iron-deficiency anæmia in the island—up to 30% among children—in the words of the report, 'the population can ill afford to wash away the nutrient value of its staple food'. Another interesting point brought out in this report is that a recent survey in Basutoland revealed that 41% of those examined suffered from endemic goitre.

SUNBATHING AND MYOCARDIAL INFARCTION

THAT 'prolonged bare exposure to extreme heat from the sun, even without physical exertion, predisposes certain individuals to the development of myocardial infarction', is the view propounded by J. C. Ham and A. M. Paull (*R.I. med. J.*, 1958, **41**, 543). In support of this thesis they give the details of a 50-year-old man with no previous history of coronary disease who on two successive occasions was admitted to hospital with an electrocardiographically confirmed myocardial infarction. Each episode was preceded by a period of sunbathing, during which the patient perspired freely, and subsequently felt chilly. The authors conclude: 'Whatever the factors may or may not be, we know of no beneficial effects from deliberate, prolonged sedentary sunbathing of the human body that warrant continuation of such a practice. This does not imply that moderate sunbathing is detrimental'.

PORCINE ACUPUNCTURE

IT is not only in human medicine that the Chinese are reviving interest in what to the Westerner is always the most traditional form of Chinese therapy—acupuncture. According to a report in the *Chinese Medical Journal* (1958, **77**, 518), it has been used with success at the Kiangsi Agriculture College in the treatment of pig asthma, a condition which is taking such a heavy toll in China that it is proving a serious obstacle to large-scale pig breeding. Of 21 serious cases treated by acupuncture within a period of a month, 19 were cured. One of the great advantages of this method of treatment, of course, is that it is so simple, two or three applications being said to effect a cure in most cases.

PLODDING MAN

'IT is a mistake to consider Man at the pinnacle of the animal kingdom on physical grounds; far from it. If an Olympic Games were organized, open to all vertebrates, Man would take a very humble place. In running, the sprint would be won by a cheetah, the mile by a gazelle, the long distance marathon by a wolf, the high jump by a kangaroo, fast swimming by a dolphin, endurance under water by a whale, high diving by a gannet, long distance vision by an eagle, keenness of scent by a hyæna, speed through trees by a gorilla and so on; Man would not gain even a bronze medal'.—Sir Victor Negus: 'Comparative Anatomy and Physiology of the Nose and Paranasal Sinuses'.

ARSENIC AND CIGARETTES

CIGARETTES contain fourteen times as much arsenic as is permitted in food, and the increased use of arsenic on tobacco plantations has paralleled the rise in the incidence of carcinoma of the lung, according to a report that has just been published in the United States. The report concludes: 'Although the evidence linking the arsenic in cigarette smoke to lung cancer is highly suggestive, it is felt that a sober approach to the problem with clinical and laboratory studies is needed to prove or disprove the hypothesis'.

IRAQ AND DRUG ADVERTISEMENTS

THE Board of Trade has announced that the following 'Notification' has been issued by the Iraq authorities: 'To all drug-store owners—In the interest of public health it has been decided to ban the advertisement of drugs and pharmaceutical products in local papers and publications, and in public places'.

PUBLICATIONS

Poliomyelitis consists of the papers and discussion presented at the fourth international poliomyelitis conference held in Geneva in 1957. It provides an admirable review of our knowledge of the disease up to that date. (Pitman Medical Publishing Co. Ltd., price 60s.)

Clinical Side Room Methods, issued by the Standing Committee on Laboratory Methods, University of Glasgow (Convenor, E. J. Wayne, M.D., F.R.C.P.), in its seventh edition is the successor to 'Notes on Clinical and Laboratory Methods', published with the aim of ensuring uniformity in the clinical side-room methods employed in the Glasgow teaching hospitals. The text has been revised, methods for examination of blood have been brought up to date and it includes methods and reagents employed with the Lovibond comparator and a section on care of the microscope. The book is a useful guide for medical students and nurses, but too elementary for resident medical officers and postgraduate students. (John Smith & Son (Glasgow) Ltd., price 9s.)

Speech Recovery After Total Laryngectomy, by C. J. Hodson, F.R.C.P., D.M.R.E., F.F.R., and Miss M. V. O. Oswald, F.C.S.T.—This small book will be of the greatest interest to speech therapists and to laryngologists who have to do with the rehabilitation of patients after total laryngectomy. Dr. Hodson gives an account of the radiological investigation of the mechanism of voice production using cinematography. It was found that fluent speakers inspired air into the œsophagus. On its expulsion sound was produced by pseudo-vocal cords of either a sphincter-like mechanism 1 or 2 cm. long, or a narrowed segment 4 to 8 cm. long at the upper end of the œsophagus. Miss Oswald explains how these findings caused a change in the methods of speech therapy with good and quicker results. (E. & S. Livingstone Ltd., price 2*s.* 6*d.*)

Health in Industry, by Donald Hunter, C.B.E., M.D., F.R.C.P.—Here at last is a small and readable book which contains all the useful things the practitioner should know about industrial medicine. 'By visiting the places where his patients work . . . he will understand their problems better . . . '. The senior physician of the London Hospital has found time to visit the places where his patients work and so can others. The knowledge of work—one-third of patients' lives—and understanding of the patients themselves derived from such visits are expressed in this book. Chapters on details of industrial poisoning provide useful information. Many patients cannot be adequately treated unless the practitioner has a sympathetic knowledge of their working circumstances, and here is a friendly and informative guide, who can also be entertaining. At four shillings the book is practically free; it can lead to one of the best things in life—a new interest in his patients—for the discerning practitioner. Dr. Hunter has performed a lasting service for medicine. (Penguin Books Ltd., price 4*s.*)

Joint FAO/WHO Expert Committee on Nutrition. Fifth Report. WHO Technical Report Series No. 149.—We are sometimes told that nutritional problems no longer exist. Or we are told that they exist but have simple solutions—such as plankton, or oral contraception. What the true position is can be more realistically assessed from this report. Here one can see both the intricacies of the problem, and the concerted efforts by a wide variety of specialists to solve them. (H.M. Stationery Office, price 3*s.* 6*d.*)

Moral Responsibility in Clinical Research, by D. MacG. Jackson, M.D., F.R.C.S., is a thoughtful review of a problem of growing interest in these days of intensive clinical research. (The Tyndale Press, price 6*d.*)

OFFICIAL PUBLICATIONS

The Health of the School Child, the report of the chief medical officer of the Ministry of Education for 1956 and 1957, marks the jubilee of the School Health Service. The emphasis is therefore upon the striking advances in child health which have occurred during these fifty years. The major killing or crippling diseases of the Edwardian era—tuberculosis, rickets, rheumatism and malnutrition—have either been eliminated or are well on the way to disappearing. In their place, the major problems facing the Service today are accidents, which kill twice as many children as die from disease, dental caries, and delinquency—the number of children charged before the Juvenile Courts rose from 13,000 in 1913 to 38,000 in 1956. A curiously lingering hang-over from the 'bad old days' is the high incidence of verminous heads among children—250,000 children in 1957, representing about 4% of the total school population. (H.M. Stationery Office, price 10*s.* 6*d.*)

The Welfare of Children in Hospital, the report of a committee appointed by the Central Health Services Council, is an admirable review of a subject which has rightly received a good deal of attention during recent years. The major recommendations can be briefly summarized. Whenever possible, the sick child should be nursed at home, and more should be done to provide facilities for this, particularly in the way of home nursing. If a child has to be admitted to hospital, it is undesirable that he should be removed to a children's hospital which may be far from his home, when he could be nursed in a children's ward in the local hospital, which is in the charge of a pædiatrician visiting from a neighbouring centre. 'Unrestricted visiting'—i.e. parents being allowed into the ward at any reasonable hour during the day—should be adopted in all children's hospitals and wards. In the case of the child under the age of five, arrangements should be made for the mother to be admitted with the child—at least during the first day or two. (H.M. Stationery Office, price 2*s.* 6*d.*)

Staphylococcal Infections in Hospitals provides a comprehensive review of the extent of this problem and puts forward various recommendations for dealing with it. These include one that 'clinicians should be prepared to consider certain voluntary restrictions' in the prescribing of antibiotics. One of these is 'to abandon the widespread use of antibiotics for non-specific prophylaxis'. (H.M. Stationery Office, price 2*s.* 6*d.*)

CORRIGENDUM.—In the article by Dr. R. McLaren Todd in our December 1958 issue (p. 736), column five in the tables should read 'minims' *not* 'ml.'.

NOTES FROM THE CONTINENT

A European Newsletter

BELGIUM

The causation of cancer.—In a paper read before the 12th congress of the Belgian Association of Surgery, P. Desaive stressed the dependence of cancer upon its environment. There is no form of experimental cancer which can be said to be due solely to one single cause—whether endogenous or exogenous. A second factor, in the form of the genetic make-up of the animal, always comes into the picture. In other words, no form of cancerous growth develops unimpeded unless it takes place in a host in which favourable conditions exist in the genetic structure, the hormonal balance and the state of the tissues. This last may be favourably affected—so far as the growth of the tumour is concerned—by changes in the environment or in nutritional status, or by the intervention of chemical or physical agents. This holistic concept of malignant growth is particularly important in relation to the hormonal treatment of cancer. Unless it is clearly borne in mind that the hormonal is only one of the factors concerned, such therapy may be misapplied. What is even more important from the long-term point of view is that valuable clues may be missed unless the importance of the host-environment is always taken into consideration.

Cancer of the breast.—At the same congress considerable attention was devoted to the use of hormones in the treatment of carcinoma of the breast with metastases. Ovariectomy, adrenalectomy and hypophysectomy, according to W. Smets and P. Dor, are equally effective, both from the point of view of the degree of improvement they induce and the duration of this improvement, but each is indicated at a different age-period. Ovariectomy alone is only effective before the menopause. In the post-menopausal period ovariectomy combined with adrenalectomy is more effective. As the experts still differ as to the most favourable stage at which hypophysectomy should be performed, and as it is a procedure which carries considerable risk, including visual complications, it is recommended that it should be reserved for cases in which the favourable effects of ovariectomy and adrenalectomy are beginning to wear off, and the patient is relapsing.

H. Tagnon and W. Smets also recommend ovariectomy in the pre-menopausal cases, but their subsequent course of treatment is somewhat different. In the cases in which ovariectomy is initially successful but relapse later occurs, they recommend that the next stage of treatment should be adrenalectomy, followed, when necessary, by hypophysectomy, then androgens and finally cortisone. In cases in which ovariectomy produces no benefit, they recommend a course of œstrogens, then androgens and finally cortisone. Alternatively, hypophysectomy may be carried out, followed by androgens and then cortisone but, though the results are comparable, hypophysectomy carries a considerable operative risk. In the post-menopausal cases, they recommend the use of œstrogens initially; if this proves successful it should be followed by cortisone. When there is no response to œstrogens, treatment should consist of ovariectomy and adrenalectomy, followed later by hypophysectomy. Alternatively, hypophysectomy may be preferred as an alternative to ovariectomy and adrenalectomy. In either case, subsequent treatment consists of androgens and cortisone. In cases in which no operative interference is considered advisable, treatment consists of œstrogens followed by cortisone.

Crohn's disease.—Resection is preferable to short-circuiting in the treatment of the chronic form of Crohn's disease, according to A. Bremen and Ch. Flamand. In their view short-circuiting should be reserved for: (*a*) emergency operations on patients in whom there has not been time for adequate preoperative preparation; (*b*) the treatment of local infective complications; (*c*) as a preliminary to subsequent resection in cases which require operation for relief of intestinal obstruction. The view is expressed that all forms of surgical intervention are contraindicated in the treatment of the acute forms of the disease.

Protesting pharmacists.—Belgian pharmacists are up in arms—metaphorically, if not literally. Their criticisms are of both the Government and the doctors. The former is being accused of unnecessary delay in the payment of the sums due to pharmacists for medicines supplied to insured patients. Practitioners are under fire because of the increasing difficulty in deciphering their prescriptions. The trouble here seems to be a combination of inadequate information as to how the medicament is to be supplied, illegibility of handwriting and the

use of abbreviations which are meaningless to the dispenser. Incidentally, it will be of particular interest to British practitioners that a law has now been passed in Belgium which forbids anyone carrying on simultaneously the functions of a pharmacist and a doctor—even if he is both a qualified pharmacist and a registered medical practitioner. Doctors who own their own pharmacies have been given two years in which to dispose of these.

GERMANY

Colour psychology in hospital.—The importance of colour in hospital decoration has been stressed by C. Bonsels. In hospitals, he contends, all colour combinations should be cheerful and pleasing, thereby increasing the 'homeliness' of the ward. Among the points to which he draws attention is the effect of colour in altering the subjective appearance of a room. Thus, yellow seems to enlarge the room, red appears to make it smaller, more enclosed and agressive, whilst blue lends distance and depth. Among the practical recommendations made are that a room facing north should be painted yellow as a substitute for the sun, whilst a room that is too long can be made to appear square by painting the smaller walls darker than the others. As corridors are usually dark, they should be painted in light colours: e.g. yellow for the walls, light blue for the ceiling, and light grey for the doors. Physiotherapy departments should be painted brownish-yellow, 'inhaling rooms' in airy colours: e.g. sky-blue and yellow, bathrooms in 'beach colours' and lavatories should be painted white. To prevent unnecessary confusion, it is suggested that doors should be painted a distinctive colour, according to the purpose for which the corresponding room is used: e.g., the doctor's consulting room, the ward kitchen, the clinical side-room.

Preservatives in food.—New legislation which has recently been enacted by the Bundestag provides for considerable tightening up in the regulations controlling the addition of preservatives to foodstuffs. The use of foreign substances in the production and preservation of foodstuffs is forbidden, but exceptions may be allowed by Government decree after proof of harmlessness has been provided and accepted. The treatment of foodstuffs with ionizing or ultra-violet rays for purposes of preserving the food is also forbidden. A further ban is that on the injection or implantation into animals of œstrogens for the purpose of fattening them up. The feeding of œstrogens, however, is allowed as it is considered that this does not involve any risk to the consumer.

Control of drugs.—At a conference at Stuttgart recently considerable discussion took place over the proposed new legislation for the control of the sale of drugs. One recommendation put forward was that all new drugs should be registered at a central bureau before they were released for general use, and that manufacturers should be compelled to give full details of all the constituents of their preparations. Two further recommendations were that drugs, including those which can be obtained without a prescription, should only be sold in pharmacies, and that the hawking of drugs and their sale in automatic machines should be forbidden.

Miscellanea.—In an article on the somewhat morbid subject of 'Mortality among West German panel doctors', H. Moeller produces evidence of the increasing death rate among doctors and attributes this to the ever-increasing amount of overwork.

In 1958, 15,700 foreign students studied at 'high schools' and universities in Western Germany. This is a considerable increase over previous years, and is taken to mean that German teaching institutions are regaining their old reputation.

The sum of 62.9 million DM was allotted during 1958 by the German Research Institute for various research investigations. Among the plans for future development is the establishment of an Institute for the Investigation of Cancer. Another research allocation that has been announced recently is the sum of 500,000 DM donated by the life insurance societies for an investigation into the pathogenesis of myocardial infarction.

'Notes from the Continent' are produced in collaboration with the Editors of Bruxelles-Médical (*Belgium*), Le Concours Médical (*France*), Münchener Medizinische Wochenschrift (*Germany*), and Minerva Medica (*Italy*).

THE PRACTITIONER

Fifty Years Ago

'The dew was falling fast, the stars began to blink; I heard a voice; it said, "Drink, pretty creature, drink!" '—Wordsworth, *The Pet Lamb*

MARCH 1909

'Is drunkenness among women on the increase in England? And, if so, why?' ask 'Notes by the Way'. 'There are, of course, no tabulated figures available for answering them. All that one can say for certain is that the number of female inebriates, in both the poor and the well-to-do

Alfred Hegar, M.D. (1830-1914).

classes, is larger than it ought to be, and that no single cause can be held responsible for all the phenomena observed. Overwork among the women of the labouring classes is one of the causes suggested; but . . . the women of the same class in France work harder and drink less. The much-abused grocer's licence may be a factor; but . . . secret drinkers whose whisky appears in the grocer's bill as tea are probably not numerous. . . . The wine bars in confectioners' shops may also play their part in encouraging the evil, for well-dressed women with sodden faces are often to be seen there. . . . The real crux of the difficulty is to determine the circumstances in which the women who become drunkards first take to drink. Not until that point is settled can we attack the evil at its source'. Among probable responsible circumstances the Editor mentions ill-ventilated workrooms ('one never feels the need of an alcoholic stimulant more intensely than immediately after quitting an atmosphere surcharged with CO_2') and convalescence after childbirth: 'Nothing is more dangerous than to advise women in such a state to take a glass of wine or spirits "when they feel that they require it". . . . Many inebriates, we feel convinced, have been launched upon their course of inebriety by putting too liberal an interpretation upon loose medical advice'.

'The trustees of the London Hospital have received a benefaction which will be the more welcome because of the latitude left to the beneficiaries in dealing with it. An anonymous donor has placed £20,000 in their hands without labelling, or ear-marking, his gift in any way, except to stipulate that the money shall be invested and that the income shall be expended, not in routine teaching, but in the advancement of medical research and the promotion of higher education in medicine. It is not too much to say that the value of the gift is doubled by this absence of strict provisions as to its application. Nothing is more common than for donors to defeat the ends of charity by too precise directions'.

The first of the twelve 'Original Communications' is by Arthur E. Barker, F.R.C.S., Surgeon to University College Hospital, and is entitled 'Some Points in the Diagnosis and Treatment of "Derangements" in the Knee Joint'. D'Arcy Power, F.R.C.S., Surgeon to St. Bartholomew's Hospital, writes with his customary charm on 'Dr. Marshall Hall and the Decay of Bloodletting' (Harveian Society Presidential Address): 'Marshall Hall was one of the earlier and important members of the profession to throw doubts upon the indiscriminate bloodletting, which was a feature of medical practice at the time he was acting as President of this Society'. Sir D'Arcy refers to the bill for leeches at St. Bartholomew's: 'no less than 97,300 were used in 1832; only 48,100 were required in 1842. Last year 400 were bought'.

J. Inglis Parsons, M.D., M.R.C.P., Surgeon to the Chelsea Hospital for Women, discussing 'Injection of the Broad Ligaments with Quinine for Prolapsus Uteri', concludes that 'the operation is fairly simple, and takes only a few minutes to perform. It appears to be free from risk, if carried out properly. It causes no pain afterwards. It is more effective for its purpose than any other treatment'.

J. M. H. Macleod, M.D., M.R.C.P., Assistant

Physician for Diseases of the Skin, Charing Cross Hospital, deals with 'The Present State of Our Knowledge of Pemphigus'; Macleod Yearsley, F.R.C.S., Senior Surgeon to the Royal Ear Hospital, contributes a 'Retrospect of Otology'; G. McKerrow, M.B., C.M., and J. S. Geikie, M.B., Ch.B., deal with 'Appendicitis in General Practice'; and John Allan, M.D., Ch.B., describes 'The Treatment of Relapsing, Recurrent, and Chronic Appendicitis'.

'Notes from Foreign Journals' refer to the use of blackcurrant leaves in infusion in the treatment of chronic and subacute rheumatic affections. 'The pharmacological examination by Dr. Chevalier showed the presence in the leaves of an essential oil, which splits up into quinic acid and a very active oxydase. It appears to act as a stimulant to the renal epithelium, promoting marked diuresis with increased elimination of incompletely oxidised nitrogen'.

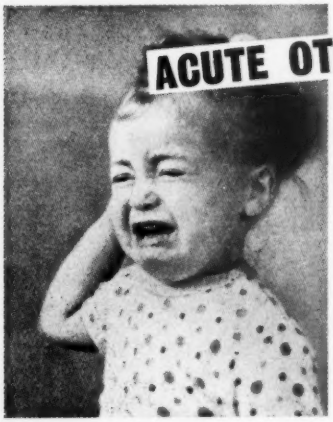
The books reviewed this month include volumes III and IV of Osler's 'System of Medicine'; H. Campbell Thomson's 'Diseases of the Nervous System'; Munro Kerr's 'Operative Midwifery'; and C. B. Lockwood's 'Clinical Lectures and Addresses on Surgery'.

'Practical Notes' describe Hegar's sign as 'the most certain of all the presumptive signs of pregnancy'. This sign, a striking example of misplaced credit for priority in original observation, was first described in 1884 by Carl Reinl, assistant to Alfred Hegar at Freiburg, and eleven years later, in 1895, by Hegar himself, who acknowledged Reinl's priority in publication. It was Hegar who taught and publicized it so that it became known by his name. The son of a doctor, Alfred Hegar studied at Giessen, Heidelberg, Berlin, and Vienna. He graduated M.D. in 1852 and from 1864 to 1904 occupied the chair of obstetrics and gynæcology at Freiburg. Pioneer in Germany of the modern operation of ovariotomy, he was a fine surgeon, a lucid writer, a popular teacher, and a tremendous worker.

'Preparations and Inventions' contain an item of historic interest: 'Glidine' (Menley & James), 'introduced to the medical profession in this country from Germany and Austria. . . . It is a vegetable protein food, prepared wholly from wheat . . . readily digested, and has a very high food value. Iodoglidine and Bromoglidine are very stable combinations of Iodine and Bromine respectively with Glidine'.

'An Ophthalmic Vade-Mecum' (Burroughs Wellcome & Co.), made in silver and metal, is described as a very useful little instrument, 'for it fills a long-felt want'.

W. R. B.



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